CLINICAL STUDIES OF ERECTILE IMPOTENCE IN DIABETIC MEN

BY

DAVID K. McCULLOCH,

B.Sc., M.B., Ch.B., M.R.C.P.

A Thesis for the Degree of Doctor of Medicine in the University of Edinburgh.

MAY 1984

UNIVERSITY OF EDINBURGH

ABSTRACT OF THESIS (Regulation 7.9)

Name of Candidate DAVID KENNEDY M°CULLOCH

Address .....

Degree DOCTOR OF MEDICINE *Date* 25th May 1984

Title of Thesis CLINICAL STUDIES OF ERECTILE IMPOTENCE IN DIABETIC MEN

The aims of this thesis were to establish the prevalence of erectile impotence in male diabetics, investigate the aetiology and follow the natural history in order to gain a fuller understanding of the condition. From a cohort of 541 diabetic men aged 20-59 years it was found that 190 (35%) were impotent. Impotence was associated with age, retinopathy and symptomatic peripheral and autonomic neuropathy. Subgroups of patients were investigated in more detail using cardiovascular autonomic function tests and by the non-invasive evaluation of bladder function. Impotent diabetic men had more abnormalities in bladder function. The severity of bladder dysfunction correlated with the degree of abnormality in cardiovascular autonomic function tests. Four hundred and sixty-six of the original cohort were followed prospectively over a five year period. Only 11 of those originally impotent had regained potency while 78 out of 275 who were originally potent became impotent. Apart from age, the most important factors, present originally which increased the likelihood of developing impotence were poor diabetic control, heavy alcohol intake and the presence of retinopathy or intermittent claudication. Sixty-three patients died, but impotence per se was not associated with increased mortality. The thesis concludes by discussing the implications of these data for the prevention and management of erectile impotence in diabetic men.

INTRODUCTION AND ACKNOWLEDGEMENTS

The concept of this thesis grew from the germ of an idea which I had during my Final Year Elective Attachment to the Diabetic Department of the Royal Infirmary, Edinburgh in the summer of 1976. At that time there was great interest in the impact of autonomic neuropathy on diabetics, and erectile impotence was considered to be one of the commoner manifestations of autonomic neuropathy in men with diabetes. Two aspects of this clinical problem stimulated my interest and prompted me to look at it in more detail. Firstly, impotence seemed to be a major source of morbidity for many diabetic men and yet the prospects for investigation and treatment were limited. Secondly, while the more florid symptoms and signs of autonomic neuropathy occurred in only a small number of longstanding diabetics with multiple complications, impotence seemed very much commoner, affecting men at almost all stages of their illness.

After discussing these issues with colleagues in the Diabetic Department, I was encouraged to document the size of the problem by doing a large randomized cross-sectional study. I am grateful for the help and advice I received from Drs Basil Clarke and Ian Campbell of the Diabetic Outpatient Department and to Dr. Robin J. Prescott of the Medical Computing and Statistics Unit.

This study generated a large representative cohort of impotent and potent diabetic men who were relatively well characterized from a clinical point of view. Several questions were subsequently posed by this study and I felt that detailed analyses of subgroups of these men would shed further light on the

aetiology of erectile impotence among these men. Several other researchers in Edinburgh expressed a great interest in becoming involved with such studies and so a group of collaborators was set-up to look into this:

Dr. Christopher Fairburn of the Department of Psychiatry, Edinburgh University and Dr. John Bancroft of the MRC Reproductive Biology Unit, Chalmers Street, Edinburgh were interested in documenting the clinical features associated with sexual dysfunction in diabetic men as a detailed description was lacking in the literature. The results of this study are shown as an appendix to this thesis.

Dr. Frederick C. Wu of the Departments of Endocrinology /Obstetrics and Gynaecology was interested in carrying out comprehensive endocrine testing among a group of these men. Unfortunately results from this work are not yet available but should add some interesting information on this complex area.

Dr. David Q. Borsey, from the Diabetic Department, Royal Infirmary, Edinburgh and Dr. David J. Ewing from the Department of Medicine, Royal Infirmary, Edinburgh, and myself as principal investigator were interested in evaluating the technique of Uroflowmetry among diabetic men to see whether this technique could be used as a simple screening test to determine whether or not impotence in any particular individual was associated with signs of bladder neuropathy. Dr. F.C. Wu was also of considerable help in this study.

Drs John Bancroft and Christopher Bell, of the MRC Reproductive Biology Unit, Chalmers Street, Edinburgh decided to look more directly at the vascular mechanisms of erection and at the psychophysiological response of potent and impotent men to visual erotic stimuli. Some data from this work are included as an appendix to this thesis.

Although I played some part in all of these studies, my major contribution was in the studies of Uroflowmetry and cardiovascular DAN testing and so, only these aspects are presented in the main body of the thesis.

Towards the end of 1980 it became clear that many features had changed among the large cohort of men. Some who were previously potent had become impotent, a few previously impotent had regained potency while several others had developed other complications or had died. I felt that a much clearer understanding of the clinical problem of impotence would be obtained if the entire cohort were reviewed again to document the natural history of the condition. I therefore reevaluated the group during 1981-82. I am very grateful to Dr. Robert J. young of the Diabetic Department, Royal Infirmary, Edinburgh for help with the data collection and analysis of this prospective study.

Throughout all this work I have found my collaboration with others stimulating and educational. I am grateful for all that I have learned. I would like to single out a few people for special thanks. Dr. Basil F. Clarke has been an immense help to me throughout the entire study. Dr. Robin J. Prescott and his Department carried out the complex computer based statistical analyses

associated with the cross-sectional and prospective epidemiological studies. it has been refreshing to work with a statistician who can make this complex field understandable to a clinician. I would like to thank Mrs. Sarah Dickson of the Diabetic Department for the tireless effort she expended in the tedious tasks of locating hospital notes without which the data collection in the large epidemiological studies would have been incomplete. I am also grateful to Ms. Jane Richards (in Nottingham) and Mr. Kris Jones (in Seattle) for their careful typing of the manuscript.

Finally, I would like to express my thanks to my wife Ishbel, and to my children, Lewis, Wendy and Roderick. They have had a lot to put up with from me in the past few years during the preparation of this thesis. Without their patience and understanding I might have given up long ago.

TABLE OF CONTENTS PAGE

LIST OF FIGURES FOLLOWING PAGE

diabetic and non-diabetic men

FIGURE 9 65

Distribution of the index F/PxV among diabetic men with differing degrees of cardiovascular autonomic dysfunction

EXPLANATION OF THE RATIONALE FOR THE STATISTICAL METHODOLOGY USED IN THE EPIDEMIOLOGY STUDIES OF THIS THESIS.

The aetiology of erectile dysfunction among diabetic men is likely to be so complex that several interrelated factors may well play a role in its development. For this reason, when trying to derive which aetiological factors are likely to be of most significance in the development of erectile impotence the most appropriate statistical method to analyze these data is by use of LINEAR LOGISTIC MODELS. To understand these one should first understand the rationale for using MULTIPLE REGRESSION MODELS, which in turn are understood best after looking at LINEAR REGRESSION. Linear and multiple regression are well described by Armitage (1971) and linear logistic modelling by Cox (1970).

LINEAR REGRESSION

Linear regression is useful if one is interested in knowing how variable y (the DEPENDENT VARIABLE) is affected by changes in x (the INDEPENDENT VARIABLE) in a population of subjects. If one assumes that y is a continuous variable, that the distribution of y, for any given value of x is normal, and that the expected (mean) value for y is a linear function of x, then we can plot the data as shown in Figure 1. The relationship of x and y is represented by a straight line such that we can predict Y_i for any value of x (say x_i):

$Y_i = a + bx_i$ where a is the intercept and b is the slope of the regression line.

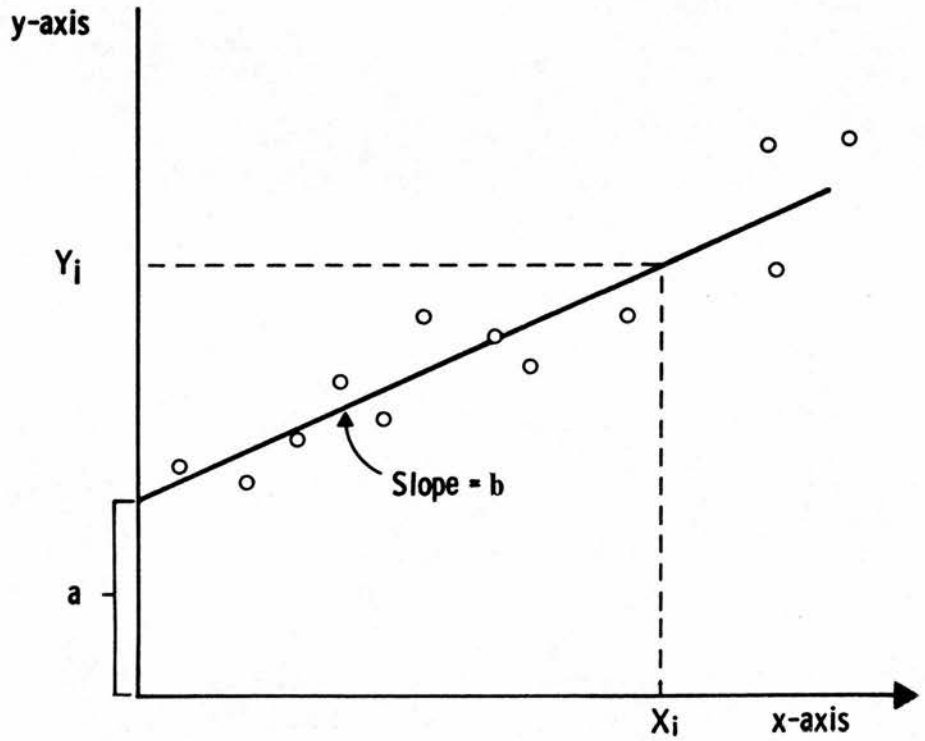


FIGURE 1 Linear regression

This methodology might be used, for example, if we wanted to look at the effect of carbohydrate intake at lunchtime on the postprandial blood glucose level. For example,

Y = blood glucose 2 hours after lunch

x = carbohydrate intake at lunch

Since both x and y here are continuous variables, and since we could measure values of x and y in a population of insulin dependent diabetics for example, we could fit a simple linear relationship as described above, assuming that the relationship is not of a more complicated form than linear.

However, in reality the postprandial blood glucose in insulin dependent diabetics could be affected by many other variables e.g., insulin dose, endogenous C-peptide level, total calorie intake, proportion of high fibre carbohydrate etc. Here, not only is there an increase in the number of variables affecting y, but, in addition, several of the independent variables x_1, x_2, etc. are in fact interrelated (e.g., the more endogenous C-peptide a patient has, the lower his insulin dose is likely to be). For these reasons multiple regression analysis is necessary to make sense of the data.

MULTIPLE REGRESSION

The purpose of this is to study the effect on variable y (the dependent variable, e.g., two hour postprandial blood glucose) of changes in several other independent variables x_1, x_2, x_3, etc. These independent variables are also

called EXPLANATORY or PREDICTOR variables. The method also takes into account the fact that changes in several of these predictor variables can affect each other.

The data to be analyzed consist of observations on a set of n individuals, each individual providing a value of the dependent variable y and a value for <u>each</u> of the predictor variables x_1, x_2,...x_p where p is the number of predictor variables. The number of predictor variables, p, should preferrably be considerably less than the number of observations, n, and the same p predictor variables must be available for each individual in any one analysis. Since the complexity of the calculations increases rapidly with the value of p, it is necessasry to employ a computer program for multiple regression analysis.

We can produce an equation, similar to the one shown for linear regression, where for particular values of x_1,x_2,...x_p the observed value of y is specified by the linear model:

$$y = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_p x_p + e$$

where e is an error term and is supposed to be independently and normally distributed with zero mean. The constants β_1, β_2, ... β_p are called partial regression coefficients and α is the intercept. Thus the coefficient β_1 is the amount by which y changes on average when x_1 changes by "one unit" <u>and when all the other x's remain constant</u>. Thus, in general β_1 will be different form the ordinary regression coefficient b (as described above for <u>linear</u> regression) because the latter represents the effect of changes in x_1 on the average values

of y with no attempt to keep the other variables constant. The coefficients β_1, β_2, ... β_p are idealized quantities measureable only from an infinite number of observations. In practice we use an estimate of the coefficients (which is acceptable, especially where n is large) and thus an estimated regression equation can be made:

$$Y = a + b_1x_1 + b_2x_2 + \ldots b_px_p.$$

The next step is to find the partial regression coefficients (b_1, b_2, b_3,...b_p) which is done using matrix algebra (Armitage, 1971, pgs. 305-310, Murphy, 1982, pgs. 200-229).

Analysis of Variance Test for deletion of variables.

Having derived values for b_1, b_2,...b_p, the t-test for any one of these partial regression coefficients (e.g., b_j) tests whether the corresponding predictor variable x_j can be dropped from the regression equation without any significant effect on the variation of y. With a large number of interrelated predictor variables it often becomes quite difficult to sort out the meaning of the various partial regression coefficients. Obviously the predictor variables themselves have to be chosen sensibly in the first place as being factors likely to affect the dependent variable y. The procedures used to find which of the variables are most significant in causing changes in y are either step-up procedures or step-down procedures. With step-up procedures the computer is asked to try each x in turn, choosing the one which provides the biggest effect on the regression in terms of minimising the residual sum of squares. It retains this

predictor variable and goes through the remainder to see which of those, when added to the retained variable gives the largest improvement to the regression. Having selected this second variable to be retained it repeats the process, adding one more variable each time until the increments by which the residual sum of squares is changed cease to be (in some sense) significant. With a step-down procedure the computer first does the regression on all predictor variables. It then does regression by dropping each variable in turn to derive a set of regressions using p-1 variables. Whichever dropped variable caused least change to the regression is eliminated as being non-significant. The process is then repeated for all the possible regressions using p-2 variables. The process stops when all the retained regression coefficients are (by some criteria) significant such that, by dropping any one of these remaining variables, the change in residual sum of squares is sizeable and thus for the best explanation of which independent variables (x's) affect changes in y, all must be retained. Both of these procedures usually (though not necessarily) converge to the same model. In the studies described in this thesis the step-up procedure was most commonly used.

The interpretation of the results obtained from this process requires some common sense. For example if we included "number of teeth" as a predictor variable for impotence we might find that there was a highly significant negative correlation between the number of teeth and the probability of impotence (!.) whereas the true explanation is likely to be that advancing age is affecting both x (number of teeth) and y (potency). However, theoretically the computer might eliminate age and retain "loss of teeth" as being one of the best predictors of potency. The techniques of multiple regression should sort out this type of

problem, however, unless the relationship between the two variables is very strong. Nevertheless, careful scrutiny of the predictor variables retained and those eliminated is therefore an essential part of the data interpretation.

LINEAR LOGISTIC MODELLING

I have attempted, in the above description, to explain why multiple regression is a more valid method of data analysis than the "one variable at a time" approach when looking at the effect of a large number of interrelated variables on the dependent variable y in which we are interested. The limitation of multiple regression analysis, as described, is that it assumes that the dependent variable y is a continuous variable which is normally distributed. While this is appropriate for the example of postprandial blood glucose given earlier, it is inappropriate where y is represented by an all-or-none, yes or no type of response. Thus in our studies, we asked patients if they "had been completely unable to achieve and maintain an erection sufficient for vaginal intercourse on all occasions during the past 6 months." The response to this was therefore yes or no. Linear logistic models were derived for this situation (Cox 1970). Thus if p denotes the probability that an individual is impotent, we fit the equation:

$$\log(p / (1-p)) = a + b_1x_1 + b_2x_2 + \ldots b_nx_n$$

where $x_1, x_2, \ldots x_n$ represent the values of our "explanatory" variables.

EXPLANATORY VARIABLES USED

Age - continuous variable, in years

Weight - $\leq$ 110% IBW

Marital status - married / other

Duration of diabetes - continuous variable, in years

Diabetic treatment - I, OHA, Diet

Alcohol intake - Grades I-IV

Retinopathy - I-IV

Nephropathy - I-IV

Peripheral neuropathy - Yes/No

Autonomic Neuropathy - Yes/No

Ischaemic heart disease - Yes/No

Intermittent claudication - Yes/No

Diabetic control - Poor/Fair/Good

The models used in our analysis were fitted using the computer package, BMDP. As acknowledged previously I am grateful to R.J. Prescott and the Department of Medical Computing and Statistics for their work in the computing of these data. The interpretation of the results was carried out by consultation between R.J. Prescott, D.K. McCulloch and I.W. Campbell during the prevalence study and between R.J. Prescott, D.K. McCulloch and R.J. Young during the natural history study.

In both the cross-sectional and prospective epidemiology papers in the thesis tables are used to illustrate the data in visual detail. The p-values shown

below each table are derived from the linear logistic model and are derived from likelihood ratio tests, based on differences in log likelihoods when a term is included and then excluded from the model. The p-values thus show the significance which that variable has on impotence, taking into account not only the data shown in the table but also incorporating the interrelationships of that and all the other predictive variables used."

REVIEW OF THE LITERATURE

INTRODUCTION

Erectile impotence is defined as the inability to achieve and maintain a penile erection of sufficient rigidity for insertion and completion of the sexual act. Its occurrence causes a great deal of misery, especially if it is unexpected, permanent and occurring at an early age. Apart from the unhappiness brought about by the loss of sexual satisfaction, impotence has more far reaching effects, causing loss of self-esteem and confidence.

The first report in the literature suggesting that sexual dysfunction could occur as a consequence of diabetes mellitus was made almost two centuries ago by Dr. John Cleghorn, lecturer in chemistry and one of the physicians to the Infirmary at Glasgow. His letter to Dr. John Rollo in May 1797 was published in Rollo's book the following year (Rollo 1798). Cleghorn described succinctly the plight of a 38 year old Glaswegian porter:

> "He is the father of several children, but since he has been seized with Diabetes - coitus nullus. Erigitum nunquam: ne quidem semel rigescit."

Several other authors in the pre-insulin era commented on the frequency of the problem (von Noorden, 1903; Naunyn, 1906). Naunyn regarded impotence as one of the commonest symptoms in male diabetics, reporting its occurrence both in patients debilitated by loss of sugar and in other patients relatively untroubled by the disease. Following the introduction of insulin in 1922 very little mention is made of impotence for thirty years. Simpson (1950) expressed the belief that persistent impotence, complained of by the patient, was not common "in patients who had always been controlled with a balanced diet and insulin." However,

when patients were asked about sexual problems directly, in formal surveys to assess the prevalence of impotence, the findings differed markedly from this view.

PREVALENCE OF DIABETIC IMPOTENCE

Several authors in the past twenty five years have found a high prevalence of impotence among diabetic men (Rubin and Babbott, 1958; Schoffling, 1960; Montenero and Donatone, 1962; Prikhozhan, 1967; Ellenberg, 1971; Faerman et al, 1972; Kolodny et al, 1974). The overall prevalence varies from 40 - 75% in these studies, the differences being largely attributable to variations in the age ranges of the subjects (Table 1) and to methods of case selection. This is much higher than the overall prevalence of 2.8% quoted by Kinsey et al (1948) for the general population.

All the studies quoted above show a marked rise in the prevalence of impotence with increasing age. There is disagreement however about the association of impotence with duration of diabetes. Schoffling et al (1960) found that the mean duration of diabetes was 9.3 years in the group of men with impotence compared with 4.3 years in a similar potent group. Other authors (Rubin and Babbott, 1958; Ellenberg, 1971; Kolodny et al, 1974) have failed to find such an association however.

Some authors have claimed that impotence bears no relationship to diabetic control (Martin, 1953; Ellenberg, 1971; Kolodny et al, 1974) but since none of these studies was prospective in nature and none used an adequate assessment of metabolic control, this lack of relationship must be regarded as unproven.

TABLE 1

Previous studies outlining the prevalence of impotence in diabetic men

AUTHOR (date)	No. OF SUBJECTS	AGE RANGE (Yr)	PERCENTAGE IMPOTENT (%)
Rubin and Babbott (1958)	198	16 - 92	55%
Schoffling (1960)	314	16 - 65	51%
Montenero and Donatone (1962)	436	20 - 65	52%
Prikhozhan (1967)	350	Not stated	75%
Ellenberg (1971)	200	Not stated	59%
Faerman et al (1972)	299	18 - 50	40%
Kolodny et al (1974)	175	18 - 81	49%

CLINICAL FEATURES OF DIABETIC IMPOTENCE

With the increasing awareness of sexual dysfunction among diabetic men brought about by these studies the clinical pattern of erectile impotence in these patients has emerged. Two forms of erectile difficulty are described. In the first, failure of erection occurs in the context of poor diabetic control. Rubin and Babbott (1958) describe how erectile failure and loss of libido accompany the general malaise and lethargy associated with hyperglycaemia and how all three reverse once the patient's physical condition improves. Kolodny et at (1974) describe how 8 out of 14 men who were impotent at the onset of diabetes regained potency following the initiation of diabetic therapy. The second and much more common form of diabetic impotence occurs gradually and insidiously in the context of established diabetes. This latter condition is often referred to as "organic impotence" which is then simplistically distinguished from "psychogenic impotence" on the basis of five or six characteristics which are believed by some to be powerful discriminating features (Cooper, 1972 - see Table 2). The features of this "organic imotence" are contrasted vividly with the features of "psychogenic impotence." In the former, impotence is said to occur gradually in diabetic men with preservation of normal libido and in the absence of psychological upset or marital dysharmony. Accompanying this erectile failure are a loss of spontaneous and morning erections and a difficulty in achieving erection during masturbation. In the latter, impotence is usually sudden in onset, intermittent and selective in expression and associated with a decrease in libido, and the presence of an obvious marital or psychological precipitant. In this situation the ability to obtain an erection spontaneously, during mastrubation, or on waking are said to be maintained. While these stereotyped clinical features have been used by some authors in the differential

diagnosis of impotence among diabetic men (Cooper, 1972; Ellenberg, 1980), their validity has recently been challenged. Several patients may show intermediate clinical features (Schiavi and Hogan, 1979) and there have been recent reports of the successful use of sex therapy in the treatment of diabetic impotence (Waxberg, 1978; Renshaw, 1979).

AETIOLOGY OF DIABETIC IMPOTENCE

Before reviewing the work which has been done to investigate the aetiology of imotence in diabetics, I would like, first, to review what is known about the mechanism by which erections are obtained and maintained in the normal human male. Neurological, endocrine, vascular and psychological factors are all involved.

Table 2

Traditional distinction made between psychogenic and organic impotence

	PSYCHOGENIC	ORGANIC
ONSET	Sudden	Gradual
PROGRESSION	Episodic and sometimes transient.	Insidious and irreversible.
INITIAL CIRCUMSTANCES	Related to marital conflict or bereavement.	Unrelated to life events.
EXPRESSION OF SEXUAL PROBLEM	Selective, with normal erections occurring in certain situations.	Total loss of erections in all situations.
MORNING ERECTIONS	Preserved.	Lost.
LIBIDO	Reduced.	Normal.

SECTION A

Mechanisms involved in normal male sexual function

(i) Neurological

At a fairly simplistic level, the neurological mechanisms involved in the normal male sexual response can be stated in the following way. Penile erection occurs as a reflex mediated by the parasympathetic nerve fibres from the second, third and fourth sacral segments of the spinal cord (nervi erigentes). Stimulation of these nerves results in dilation of the penile arteries, increase in blood flow and tumescence of the corpora cavernosa and corpus spongiosum. Detumescence results from vasoconstriction of the penile arteries with subsequent decrease of arterial blood flow, diminution of pressure and release of the compressed veins (Learmouth, 1931; Bors and Camarr, 1960). Ejaculation, on the other hand, is mediated by sympathetic nerve fibres causing forceful antegrade propulsion of fluid from the urethra to the outside, by contraction of the bulbocavernosus muscle (Whitelaw and Smithwick, 1951) while affecting closure of the internal vesical sphincter at the moment of ejaculation (Retief, 1950).

While all this is true, we are largely ignorant of the interneuronal transmitters involved in these mechanisms. Although erection is believed to be influenced by the cholinergic parasympathetic fibres described above, controlled experiments have shown that atropine does not prevent erection in man or monkey (Wagner and Brindley, 1980). More recently the neurotransmitter vasoactive intestinal polypeptide (VIP) has been demonstrated in the penis (Polak et al, 1981; Willis et al, 1981). In vitro studies of smooth muscle from the cavernous bodies of rabbit, monkey and man have shown that VIP has a relaxing effect on this tissue (Wagner, 1982). The significance of these findings is unclear

but they highlight the deficiencies in our full understanding of the neural control of erectile function.

(ii) Endocrine

An understanding of the influence of endocrine factors in the male sexual response is hampered by several problems. Firstly there is very little uniformity in the definitions of terms such as "potency" or "libido" in the published literature. Thus the adequacy of these definitions and their comparability between studies makes the interpretation of data tentative at best. Secondly it is often difficult to unravel the cause and effect relationship between sexual behaviour and hormone levels. Thirdly a considerable amount of published work draws conclusions from studies which were not adequately controlled and so it is not surprising that conflicting results are obtained by different authors.

Libido is described by Davidson, Kwan and Greenleaf (1982) as the "sum of the affective - cognitive processes which result in the tendency to engage in sexual behaviour." It comprises several elements. There is the desire for sexual activity, expressed in increased sexual thoughts and fantasies. Related to these are elements of enjoyment, pleasure or satisfaction derived from engaging in such thoughts. Finally libido is influenced by the importance which an individual attributes to his or her sexuality which is partly influenced by external pressures from society and the media. Potency, on the other hand, can be defined as "the capacity to respond to sexual stimuli (exogenous or endogenous) with physiological genitopelvic responses: primarily (a) erection and associated vasomotor activity, and (b) ejaculation and associated neuromuscular activity." Both of these terms are fairly complex. In addition, although they are often separated for purposes of clarity in data analyses they are interrelated physiologically. It is hardly surprising that no simple relationships can be found

between hormone levels and a process as complex as this.

Turning to the problem of "cause and effect," before looking at the evidence for how endocrine factors may influence sexual behaviour it is worth considering how sexual activity can influence hormone levels. There is evidence that androgen levels become elevated after sexual activity (Fox et al, 1972; Kraemer et al, 1976) and that increased plasma testosterone levels can be noted as a response to watching a sexually stimulating film (Pirke, Kockott and Dittmar, 1974). In addition, psychological stress such as that observed during stressful training of military officers has been reported to be associated with depressed testosterone levels (Kruez, Rose and Jennings, 1972). These effects may partly explain why some studies of androgen function in cases of "psychogenic impotence" have decreased testosterone in the urine (Ismail et al, 1970) and plasma (Legros et al, 1973; Raboch, Mellan and Starka, 1973). However, when precise definitions of psychogenic impotence have been used and where adequate control subjects are also studied the consensus of opinion indicates that androgen deficiency does not contribute to the development of psychogenic erectile impotence (Lawrence and Swyer, 1974; Ansari, 1975, Comhaire and Vermeulen, 1975; Schwartz, Kolodny and Masters, 1980; Pirke and Kockott, 1982).

This problem of "cause and effect" is also difficult to unravel when looking at the influence of hormone levels on the well-known downward trend in sexual function with advancing age shown both in the normal population (Kinsey et al, 1948) and in diabetics (see Table 1). Advancing age is associated with a decrease in plasma testosterone, an increase in sex hormone binding globulin and an increase in gonadotrophins (Vermeulen, Rubens and Verdonck, 1972; Baker et, 1976; Stearns et al, 1976). However, although a correlation can be shown

between hormonal levels and behavioural variables such as libido and performance, as assessed by questionnaires, the relationship is not strong and the effect of androgen replacement in this situation is not impressive (Davidson, Kwan and Greenleaf, 1982).

Studies of the sexuality of human castrates should shed some light on the influence of androgen levels on sexual function. Unfortunately well designed studies are lacking and thus only very broad conclusions can be drawn. Several studies have shown that sexual behaviour is drastically reduced or completely suppressed in a high percentage of castrates (Stone, 1932; Bremer, 1959; Langeluddecke, 1963; Mitamura, 1970; Cornu, 1973; Heim and Hursch, 1979; Heim, 1981). However it is of interest to note from these studies that a proportion of castrated men retain a significant degree of sexual function and that, in general, erectile potency is less affected by castration than sexual interest and libido.

Similar distinctions have been made with regard to the effect of androgen replacement on the sexual function of hypogonadal men. While several studies show a significant relationship between changes in testosterone levels and changes in several elements of sexuality, the effects on libido and the frequency of sexual thoughts are much quicker while the improvement in erectile and ejaculatory function follows afterwards. There is some evidence that decrease in testosterone levels leads to a waning of sexual thoughts and fantasies and that erectile and ejaculatory problems are largely secondary to this. It has been noted in 8 hypogonadal males (including 2 castrates) that the erectile response to visual erotic stimulation was no different when taking androgen replacement than without, and indeed was not significantly different from normal controls (Bancroft and Wu, 1982). However these men showed an impaired erectile

response to fantasy when off replacement therapy which was restored after treatment, suggesting that testosterone may have more effect on cognitive aspects of sexual function and that erectile responses may be secondary to these. Davidson, Kwan and Greenleaf (1982) claim that, not only is the erectile response during erotic films normal in castrates and hypogonadal men but that detumescence after the film has finished is slower. They conclude that the main influence of testosterone is to stimulate cognitive acts involved in the generation of sexual imagery or to facilitate the awareness of genital stimulation.

In conclusion, there is strong evidence that endocrine factors have a major modulating effect on the basic male sexual response. However, because of the complexity of the interrelationships between the sexual activity and the endocrine system, the diagnostic value of single measurements of plasma or urinary hormone levels is limited.

(iii) Vascular

There is no doubt that an adequate arterial blood supply to the penis is necessary for the development and maintenance of a normal erection. The first clinical demonstration that arterial occlusion could result in erectile failure was made by Leriche (1940) who described a syndrome characterized by ischaemia of the lower limbs and erectile impotence following occlusion of the aorto-iliac bifurcation. Further evidence came in 1958 when O'Connor reported a case of Leriche syndrome where endarterectomy of the aortic bifurcation resulted in restoration of sexual activity. Although several larger series have suggested that improved potency occurs in only a small proportion of patients (Harris and Jepson, 1965; May et al, 1969; Spiro and Cotton, 1970) the importance of an adequate vascular supply for erectile function is indisputed. A rare, but

dramatic piece of supporting evidence for this is the "pelvic steal syndrome" (Michal et al, 1978; Metz and Mathiesen, 1979; Queral et al, 1979). In this syndrome the patient is able to achieve and maintain an erection at rest but immediately after commencing coital movements he develops pain in the gluteal muscles and detumescence of the penis. Once again, restoration of potency has been described after reconstructive vascular surgery in such cases (Michal et al, 1978).

Recently attempts have been made to quantify the extent of proximal vascular insufficiency. The simplest of these methods is the measurement of systolic blood pressure in the penile arteries measured in the flaccid state by placing a small cuff round the base of the penis and detecting the return of systolic pulsation using a Doppler ultrasound technique. The values obtained are compared with the systolic pressure in the arm, and expressed as a ratio - the penile - brachial pressure index (PBPI). When using this technique among patients known to have proximal aorto-iliac occlusion and associated impotence, a PBPI of less than 0.6 suggests an arterial cause for the impotence while ratios greater than 0.75 make an arterial cause less likely (Gaskell, 1971; Engel et al, 1978; Queral et al, 1979). However, in conditions where more distal atheromatous occlusion is likely (notably in diabetes) the interpretation of the PBPI must be more cautious.

Michal et al (1976) have pioneered a more invasive technique in order to obtain more detailed information about the haemodynamic changes surrounding impotence. Phalloarteriography is a technique by which selective arteriography of the hypogastric arteries is performed while, at the same time artificial erection is induced by infusing heparinized saline directly into the cavernous bodies. Apart from allowing good visualisation of the penile arterial bed, the

technique also allows measurement of intracavernous pressue and penile circumference during erection along with an estimate of the flow rate necessary to maintain erection. Although this technique is indeed invasive, and requires local or even general anaesthesia, Michal claims that it is well tolerated and may even lead to an improvement in erectile capability lasting for several days, at least, in about 20% of cases. This technique of selective arteriography, with or without the addition of artificial erection has confirmed that distal arterial occlusion is commonly associated with impotence (Ginestie and Romieu, 1976; Michal, 1976) although this had been shown indirectly much earlier using impedance plethysmography (Canning, 1963).

The intricate mechanisms by which arterial input and venous outflow from the penis are co-ordinated to produce a normal erection have only been unravelled to some extent in the past decade. Up until recently the dominating theory was the "polster theory." This was initiated by the German anatomist von Ebner (1900) who described specialised "pads" or "cushions" of smooth muscle inside the vessels of the penis. Kiss (1921) agreed with von Ebner's findings as did Conti (1952) who coined the term "polster." These observations were purely anatomical however and the explanation of the physiological function of these polsters in influencing blood flow in the penis was only theoretical. Several investigators have challenged the theory that such polsters act as valves regulating penile blood flow. (Newman and Morthup, 1981; McConnell et al, 1982; Wagner et al, 1982). It is thought that these "polsters" are either age-related or pathological and that similar lesions may be found in other organs of the body (Wagner, 1982). A more plausible theory is that there are large shunt-vessels leading from the deep penile artery through the tunica albuginea into the spongiose vessels which lead back to the venous system. These shunt vessels

have been demonstrated as vascular casts (Wagner et al, 1982) and are shown to be muscular helicine arteries which are capable of dilation or constriction under neural control. It is thought that these remain open when the penis is flaccid but that they contract following erotic stimulation and thus prevent a run-off of blood into the venous system. In this situation the arterial blood is diverted into the cavernous bodies leading to penile erection.

(iv) Psychological

Although it is possible to describe the male sexual response purely in terms of neurological and vascular mechanisms there is no doubt that voluntary or involuntary cortical influences can have a profound modulating effect on these basic reflexes. Thus "psychogenic impotence" can be considered to be the result of cortical inhibition during the early excitement phase of the sexual response (Kaplan, 1974). It has been estimated that up to 90% of cases of erectile impotence in the general population are caused largely by psychological inhibition of this sort (Wershub, 1959; Masters and Johnson, 1970; Kaplan, 1974; Levine, 1977; McCary, 1978).

During the past fifteen years there has been more careful analyses of the factors associated with psychogenic impotence leading to a clearer description of the problem and allowing a more rational approach to treatment. Erectile dysfunction can be classified as primary (where the man has never been able to achieve or maintain an erection long enough to have intercourse) and secondary (where the man has had at least one successful coital experience but is now unable to have an erection). Primary erectile dysfunction is rarer, more difficult to treat and has different psychological associations than secondary erectile dysfunction. In the primary disorder there is frequently a history of strict parental attitudes in childhood, religious stringency, traumatic childhood

experiences, homosexual involvements or emotionally scarring first sexual encounters (Masters and Johnson, 1970; McCary, 1978). Masters and Johnson have consistently observed two characteristics in virtually all the cases of primary erectile dysfunction: fear, and an unusual sensitivity to unknown psychological factors that apparently would not affect other men in the same way.

With secondary erectile dysfunction the commonest finding is of extreme anxiety. This anxiety, in turn, is usually a manifestation of fear, guilt and anger. The commonest fear is the fear of failing to give the partner sexual satisfaction (sometimes called "performance anxiety") and often stems from the man having inappropriate expectation based on cultural myths and sexual ignorance. Other fears include the fear of injuring the partner, getting her pregnant, or being discovered in the act. Anxiety stemming from guilt may be due to extramarital affairs, shame and self-degradation about sexual experiences, and again, religious orthodoxy. Anxiety can also result from anger about marital arguments. The man's anger may reduce his interest in sex, or cause him to rush through the sexual act, partly through lack of interest and partly to punish his partner. She in turn may build up resentment and anger at being unsatisfied thus creating a stage for a deteriorating relationship. In this situation it is thought that erectile dysfunction may be an unconscious way of getting even with the partner. At a conscious level, he cannot be blamed because erection is an automatic response.

Levine (1976) identifies several other emotional or intrapsychic themes that may be present in men with secondary erectile dysfunction. Some men separate lust and affection, such that "sexual women" are derogated but exciting while their wife is adored but not arousing. Also, the combination of a timid

ineffectual man, lacking in self-esteem and self-assertion, and an insensitive and dominant sexual partner may commonly lead to psychogenic impotence. Some men may not be able to have erectons without unusual forms of sexual behaviour or fantasies. Others may be inhibited by guilt and anxiety stemming from previous pleasurable homosexual experiences.

Thus there are a wide variety of situations where erectile dysfunction may develop. If there is a triggering event, such as intercurrent illness, undue fatigue or excessive alcohol intake, such that a man notices, on one occasion that his sexual performance has fallen below whatever standards he believes to be normal, then his ability to accept this single episode of failure will depend on the psychological background described above, and, above all, his partner's response to his "sexual failure." If the man's anxiety is not alleviated by the time of his next sexual attempt then he may become anxious due to an expectation of failure and may concentrate his attention on evaluating his performance during lovemaking rather than relaxing and participating in the sexual act. Masters and Johnson (1970) refer to this as "taking the spectator role."

It is clear then that even in the absence of any organic damage to the genitals many factors in the psychological makeup of a man may contribute to the problem of erectile impotence. Appropriate treatment requires firstly a clear understanding of the psychological background and an evaluation of the attitudes of both sexual partners to it. The main goals of treatment are then to decrease performance anxiety by trying to remove the man's fear of failure, reorientate his emotions and sensations towards "participation" and away from "spectatoring" and finally trying to remove the woman's fear of the man's dysfunction. Although treatment can be attempted without the participation of the female sexual partner, the outcomes are significantly better when the woman is included (Cooper, 1971; Kaplan, 1974).

SECTION B

Factors involved in sexual dysfunction among male diabetics

Varying amounts of attention have been focussed on the four main aspects of sexual physiology described in Section A in studies to investigate the aetiology of impotence among diabetic men.

(a) Neurological factors

Several studies have shown an association between impotence and the presence of neuropathy in diabetics (Rundles, 1945; Martin, 1953; Ellenberg, 1971; Faerman et al, 1972; Kolodny et al, 1974; Jensen et al, 1979) although most of the supporting evidence for these claims are indirect. Abnormalities in bladder structure (Faerman et al, 1972) and function (Ellenberg, 1971) have been demonstrated in impotent diabetics, and since the bladder is subserved by the same sacral parasympathetic fibres which cause penile erection, damage to these fibres has been suggested as the explanation for coincidental bladder and sexual difficulty in these men. More direct evidence for autonomic nerve damge was found by Faerman et al (1974) when they demonstrated histochemical abnormalities in the autonomic fibres of the corpora cavernosa of five impotent diabetic men whereas no abnormalities were present in five potent, non-diabetic controls. Melman and Henry (1979) found lower noradrenaline concentrations in the spongy erectile tissue of impotent diabetic men when compared with non-diabetic controls. Unfortunately neither of these studies used potent diabetic men as a control group. Despite these criticisms, however, there is compelling evidence that pelvic autonomic nerve damage is a major contributing factor to erectile impotence in some diabetics. One apparent anomaly is that impotence is very much more common than any other features of autonomic neuropathy, and a large number of patients present with impotence as an isolated feature.

Ewing et al (1980) found that when some of these men were followed prospectively, a substantial number developed symptoms of more widespread autonomic neuropathy which can be verified by objective testing of autonomic function. It has been shown in the cardiovascular system that the parasympathetic fibres are damaged earliest and that sympathetic damage occurs at a later stage (Ewing et al, 1981). It may be that the long parasympathetic fibres to the pelvic organs are the most vulnerable fibres of all and so erectile impotence is the most common early feature of neuropathic damage in diabetics.

(b) Endocrine factors

Experimental studies with animal models have found a reduction in androgen production, Leydig cell numbers and LH receptors, and this reduction is not only proportional to the duration and severity of hyperglycaemia, but is also reversed by insulin administration (Hunt and Bailey, 1961; Foglia et al, 1969; Charreau et al, 1978; Paz et al, 1978).

Early clinical studies suggested that patients with diabetic impotence had a reduced Leydig cell number and a diminished excretion of urinary metabolites of testosterone (Schoffling et al, 1963). However, Faerman et al (1972) found no abnormalities in Leydig cell number and morphology in the testicular biopsies of seven impotent diabetic men. Furthermore, they found that in vitro testicular metabolism of ^{3}H pregnenolone was no different between these patients and five control subjects with varicocoeles. Several other workers have supported this view by finding no difference in mean plasma testosterone concentrations between impotent and potent diabetic men and normal controls (Kent, 1966; Ellenberg, 1971; Kolodny et al, 1974; Wright et al, 1976 and Jensen et al, 1979).

Recent studies have indicated that the picture is more complicated than

previously envisaged. Geisthovel et al (1976) found that impotent diabetic men had a significantly lower free plasma testosterone and an impaired HCG response compared with potent diabetic controls and Daubesser et al (1978) found diminished total plasma testosterone in both diabetic and non-diabetic impotent men compared with potent controls. On this basis the latter group suggested that Leydig cell abnormalities might be secondary to the low coital frequency of impotent subjects. However, other studies have found low plasma total and free testosterone levels in diabetic men as compared with normal controls, irrespective of whether or not there were sexual problems (Shalwan et al, 1978; Gattucio et al, 1979; Ando et al, 1979). The latter studies suggest that abnormalities in Leydig cell function may reflect the duration and severity of metabolic disturbance and its treatment, while the association with erectile impotence and other sexual problems might merely be coincidental.

Reports on the hypothalamic pituitary function of diabetic men have been no less confusing. Again Schoffling's group provided the initial impetus by demonstrating lowered total urinary gonadotrophin activity in some impotent diabetic men. However, radio-immunoassay studies found normal basal levels and an intact response to GRH stimulation both among impotent and potent diabetic men (Rastogi et al, 1974; Daubesser et al, 1978; Jensen et al, 1979; Gattucio et al, 1979). Distiller et al (1975) found an impaired LH response to GRH stimulation despite normal basal gonadotrophin levels. This finding has been subsequently confirmed by other investigators who have also reported a similar decrease in the LH response of impotent and potent diabetic subjects (Wright et al, 1976; Shalwan et al, 1978). However, Ando et al (1979) found high basal LH levels and a prolonged response to GRH stimulation in young diabetic men with good glycaemic control.

Hyperprolactinaemia has been found to be associated with impotence in some non-diabetic men (Thorner and Besser, 1977; Franks et al, 1978; Nagulesparen et al, 1978). However, there have been conflicting reports of prolactin levels in diabetic subjects. Hunter et al (1974) found high mean random prolactin levels in 10 diabetic patients without retinopathy with normal levels in four patients with retinopathy. Other groups, however, have found normal basal prolactin concentrations in insulin-dependent diabetic men with or without retinopathy (Harter et al, 1976; Froland et al, 1977; Champeyroux et al, 1978). More recently, Lester et al (1981) found no significant difference between the mean serum prolactin concentrations of 19 impotent diabetic men compared with 64 potent diabetics.

In view of the conflicting results obtained in all areas of endocrine research in diabetic men it is difficult to evaluate the relevance of hormonal factors to the sexual problems of diabetic men. Overall it seems that the changes that have been demonstrated may not be of primary aetiological importance since similar changes are encountered among potent diabetic controls. However, the relationship between individual aspects of the male sexual response (erection, ejaculation and sexual appetite) and these hormonal changes has yet to be explored. Furthermore there has been a failure to take account of variables such as the quality of metabolic control, the subject's age and treatment, and cyclical variations in testosterone and gonadotrophin levels. From a more practical point of view, however, the fruitless attempts to treat diabetic impotence with hormone replacement therapy (Ellenberg, 1971; Cooper, 1972; Kolodny et al, 1974) would suggest that endocrine disturbance is not of prime aetiological importance in this condition.

(c) Vascular factors

The significance of structural vascular disease to the erectile problems of diabetic men is difficult to assess. Since it is well known that atheroma is commoner among diabetics, occurs at a younger age and extends into more distal arteries than in the general population, it would be surprising if arteriopathy did not play a major role in "diabetic impotence." Histological studies have confirmed that diabetic males have more severe narrowing and occlusion of the hypogastricocavernous inflow to the penis than do age matched non-diabetics (Ruzbarsky and Michal, 1977). Unfortunately no study has compared the histological appearances between impotent diabetics and potent diabetics, matched for age and duration of diabetes. Without such a control group it is almost impossible to say whether the changes seen reflect the diabetic process, per se, with erectile impotence being an unrelated coincidental finding, or whether the arteriological abnormalities seen do indeed have a causative association with impotence. This same problem makes it difficult to interpret much of the data obtained from clinical investigations. Penile blood pressure studies have suggested that the penile blood supply is impaired in many cases of diabetes (Gaskell, 1971; Abelson, 1974; Engel et al, 1978; Karacan, 1980) and such findings can sometimes be confirmed by arteriography (Engel et al, 1978) or phalloarteriography (Michal, 1982). The interpretation of these findings is hampered not only by the lack of appropriate control subjects but also by the fact that many of the impotent diabetic men who show the worst vascular pathology also have severe peripheral and autonomic neuropathy (Michal, 1982). Depending on the bias of the investigator/author these findings are interpreted as either showing that arteriopathy is the major cause of diabetic impotence, though some patients have coincidental neuropathy, or as showing quite the reverse. It seems naive to look at "diabetic impotence" in this way. Both

vascular and neuropathic factors may interrelate in that arterial input and venous drainage from the penis are influenced by autonomic reflexes so that damage at several points could lead to erectile dysfunction.

(d) Psychological factors

It is surprising how little attention has been paid to psychological factors in the sexual difficulties in diabetic men. After all, diabetics are unlikely to be immune from the complex problems, described already, which can promote or aggravate sexual difficulty. In addition, diabetes, especially the insulin dependent type is a stressful illness imposing social and financial handicaps. Not surprisingly, several studies have shown that diabetes can have a profound psychological effect, not only on the individual but on his inter-personal relationships and family functioning (Treuting, 1962; Hauser and Pollets, 1979; Anderson and Auslander, 1980, Tattersall and Jackson, 1982). While much of this work has focussed on the problems of diabetic adolescents, in a study of 112 adults who had had diabetes for 25 to 48 years, Murawski et al (1970) using the Minnesota multiphasic personality inventory found that the entire sample, whether they had complications of diabetes or not, had a high depression score. They also expressed pervasive feelings of pessimism, hopelessness and depression in their test responses.

Until recently the assessment of whether or not a diabetic man had an "organic" or "psychogenic" cause for his sexual dysfunction was based on a fairly brief history, elucidating the distinguishing features outlined in Table 2. Since 1975, however, there have been several reports claiming that a more objective method of distinguishing between the two is by the measurement of erections during sleep (Fisher et al, 1975; Karacan et al 1975, 1977 and 1978; Fisher et al, 1979; Hosking et al, 1979). This work was initially based on some established

observations, but the applications of this technique to the differential diagnoses of diabetic impotence has required some quite sweeping assumptions. It has been known for 40 years that erectile episodes lasting for about 25 minutes and recurring about every 85 minutes are a normal occurrence in males (Ohlmeyer et al, 1944). These were found to be related to episodes of rapid eye-movement (REM) sleep and to exhibit a predictable pattern with increasing age. The maximal increase in penile diameter, the frequency of erectile episodes and the total amount of time where erections are present during the night (the total tumescence time) all peak after puberty and in early adult life but decline thereafter (Karacan, 1976). Despite this careful work and also some evidence that anxiety may inhibit sleep-related erections (Fisher, 1966; Karacan, 1966) one of the big assumptions which is made when using the measurement of nocturnal erections to distinguish between psychogenic and organic impotence is that in the former, REM associated erections will be normal (in marked discrepancy with the patient's daytime performance) while in the latter, such REM-associated erections will be markedly reduced in amplitude, frequency and duration. Problems of interpretation have been discovered as this technique has become more widely used. Some authors have based their findings on the absolute change in penile diameter, regarding an increase of greater than 15-16 mm as being normal (Karacan et al, 1978; Hosking et al, 1979). One problem with this is that the interindividual variation in penile size and in diameter change associated with full rigidity is large and so interpretation based on absolute changes may be misleading. It has been found that the discriminating power of this test is increased if note is also taken of duration of maximum erection, frequency of erectile episodes and total tumescence time (Fisher et al, 1979). In addition, both Fisher and Karacan suggest that the rigidity of the penis

associated with a certain change in penile diameter shold be verified either manually by an independent observer, or by measuring the "buckling pressure" (Karacan, 1980)

Another problem with the technique of measuring nocturnal penile erections has been the lack of validation of the methodology. Marshall, Surridge and Delva (1981) carried out independent assessments on 27 impotent men, based on medical and psychiatric history and placed them into one of four categories - organic, psychogenic, mixed aetiology and uncertain. They then measured the nocturnal erection pattern in these subjects and scored the results blindly. They found that they could pick out psychogenic impotence in 80% of cases when using maximum change in erection only, but that accuracy increased to 95% when they also included data on the frequency of erectile episodes. In a recent review, Schiavi and Fisher (1982) go further and suggest that interpretation is made most accurate when there is concurrent EEG and psychophysiological measurements, when measurements are done on 2 or 3 consecutive nights, when 2 strain gauges are used (one at the base of the penis and one behind the glans) and when verification of rigidity is carried out by an independent observer. All of these suggestions will undoubtedly increase the discriminating power of this procedure. Unfortunately they also argue against the use of this technique as a simple discriminator which can be used in a general medical ward, or even at home (Bohlen, 1981).

NATURAL HISTORY OF DIABETIC IMPOTENCE

For a full clinical description of diabetic impotence it is necessary, not only to establish the prevalence and investigate the aetiology, but also to follow the natural history of the condition. Ewing et al (1976) first pointed out that the presence of damage to the autonomic system in diabetics, as judged by abnormal

autonomic function tests, was a grave prognostic feature. More recently this group have published a 5 year follow-up of 73 diabetics (Ewing et al, 1980(a)). This included a group of 14 men with impotence as an isolated feature, all of whom had normal cardiovascular autonomic function tests (Ewing et al, 1980(b)). When followed for five years, 6 of these men still had impotence as their only symptom and all 6 had normal autonomic function tests. Five of the remaining 8 had died during this period of whom 3 developed other symptoms of autonomic neuropathy before death.

CONCLUSIONS

While much research has been carried out on various aspects of impotence among diabetic men particularly during the past thirty years, there are several areas where the clinical descriptions of the condition are unclear or disputed. A large and unbiased epidemiological study to establish the prevalence of the condition at the present time is needed. To plan the appropriate management of these patients it is also necessary to clarify the relative importance of the aetiological factors pertaining to particular patients. Finally, the untreated natural history of a large group of impotent diabetic men remains to be established and would allow a more appropriate selection of cases for treatment.

AIMS OF THIS THESIS

My first aim was to estimate the prevalence of erectile impotence among the population of patients attending the Diabetic Department of the Royal Infirmary, Edinburgh and to compare this with a local control population. Having identified the size of the problem I wanted to investigate the likely aetiology of erectile impotence in diabetic men, by looking at subgroups of patients in more detail. As has been already stated, many of these investigations were collaborative and so not all of the data derived from these studies are

appropriate to be presented in this thesis. Finally I wanted to follow a large group of diabetic men prospectively to determine the natural history of erectile impotence and to identify factors associated with the development of impotence de novo among potent diabetics.

Subsequent chapters of this thesis will outline the results of my studies in these areas.

THE PREVALENCE OF DIABETIC IMPOTENCE

INTRODUCTION

The aim of this study was to establish the prevalence of erectile impotence in the large clinic population attending the Diabetic Clinic of the Royal Infirmary, Edinburgh. As discussed before, many of the previous studies have produced widely differing estimates (Table 1). These occur because of differences in definition of impotence, methods of case selection and age range of patients studied. For these reasons I planned to use a strict definition of impotence and to interview a large and randomly selected group of patients within a limited age range.

PATIENT SELECTION

During the 9 month period from June 1976 to March 1977, 563 males attending the Diabetic Out-Patient Department were interviewed. A total of 132 clinics were covered and at each clinic every male aged between 20 - 59 years was included. After three months an initial group of 319 men (Group 1) had been interviewed. Since this group comprised unselected consecutive attenders at the clinic it was decided to interview a random group of approximately 100 men to exclude the possibility of bias in the original group. The total clinic male population aged 20 - 59 years was 887 and from the remaining 568 patients who had not yet been interviewed a random sample of 101 men (Group 2) was drawn who were subsequently interviewed over a six month period. Over this latter period a second non-random group of 121 men (Group 3) who were attending the clinic and not included in the random sample were also interviewed.

The total number of men included for study was thus 541, representing 61% of the male clinic population aged between 20-59 years. A further 22 who were

unable to give staisfactory interviews were omitted: in the two non-random groups (Group 1 and 3), 9 were mentally defective, 2 had cerebrovascular accidents with dysphasia and 2 were unable to speak English; in the random group (Group 2) 5 had recently left the area, 1 was hospitalized elsewhere, 2 were mentally defective and 1 had a cerebrovascular accident.

METHODS

Each subject was interviewed on his own in a counsulting room within the normal diabetic clinic. The interview was semi-structured and the data collection sheet is shown in Appendix A.

Details were obtained about the patient's age, age at onset of diabetes, height, weight and standard wt. (Metropolitan Life Insurance Tables, 1959).

Diabetic Treatment

The precise doses and names of oral hypoglycaemic drugs and insulin were noted. However, for subsequent analysis treatment was categorised as insulin, oral hypoglycaemic agents (O.H.A.) or diet alone.

Other Drug Therapy

A note was taken of all other drugs which the patient was taking. Each of these was given a code number with a view to incorporating certain drugs or drug groups in the subsequent multivariate analysis. However it was found that so few of the patients were taking other drugs that such analysis would be meaningless. This information was valuable, however, in pointing out alternative causes of sexual dysfunction in some individual cases (e.g., patient no. 2, Table 22).

Other Illnesses

Enquiry was made as to whether the patient had ever suffered from angina, myocardial infarction, cardiac failure, intermittent claudication thyroid disease

or had previously had a sympathectomy. In each case an explanation was given, in simple terms of what was meant by the term "angina" etc. If the patient said that he had suffered from any of these conditions then details were taken of where, when and how severe the illness was. Verification was made from hospital records where possible. Apart from these specific conditions each patient was asked in general about any other serious illnesses or operations. For the purposes of multivariate analyses, a clinical decision was later made on the information available as to whether significant ischaemic heart disease was absent or present.

Alcohol Intake

Each man was asked to estimate honestly, and as accurately as possible how much beer, wine, spirits or other alcoholic beverage he consumed in an average week. He was also asked if the weekly consumption had changed recently and if he had ever received treatment for an alcohol related condition.

From the raw data each patient was placed in one of four grades of alcohol consumption.

GRADE 1 ("non-drinkers") - men who took less than six alcoholic drinks throughout the year, usually limited to special occasions.

GRADE 2 ("social drinkers") - men who consumed up to 10 alcoholic drinks per week, usually on two or three nights plus occasional wine with meals.

GRADE 3 ("heavy drinkers") - men taking 3 or more drinks almost every night and often more at weekends.

GRADE 4 ("alcoholics") - men whose drinking habits were frankly outside the social norm, and those attending, previously or at present, the alcoholic treatment centre in the city. Many of these patients drank half a bottle of spirits or more per day.

Subsequently, however, for purposes of multivariate analysis grades 1 and 2 were lumped together as "MILD" drinkers and grades 3 and 4 as "HEAVY" drinkers.

Diabetic Control

Since the assay for glycosylated haemoglobin was not available in the laboratory during the early part of the study, diabetic control was assessed using clinic blood glucose results. These were mid-morning post-prandial blood samples analysed on a single-channel Beckman autoanalyzer. An average was taken from the previous 6 clinic visits and the patient was then placed in one of three categories for diabetic control:

GOOD - < 9 mmol/l

FAIR - 9.1 - 13.9 mmol/l

BAD - 14.0 mmol/l.

Retinopathy

All patients had a retinal examination in a dark cubicle with both pupils dilated. Any abnormalities, or new findings which differed from previous recordings in the diabetic clinic notes were verified by Dr. I.W. Campbell or Dr. B.F. Clarke. Retinopathy status was recorded as:

None

- no abnormalities seen.

Background

- microaneurysms and/or dot/blot haemorrhages

Exudative

- hard exudates present and/or signs of macular aedema and/or soft exudates present in addition to background changes.

Proliferative

- new vessels present on the disc or in the periphery. Patients were also included in this category if they had severe venous changes, (distended and tortuous veins with variation in calibre) or if they had evidence of previous proliferative retinopathy (scars from photocoagulation, vitreous haemorrhage, etc).

Nephropathy

All patients attending the Diabetic Department of the Royal Infirmary, Edinburgh have urinalysis at each clinic visit using "Albustix" (Ames). All previous records from each patient were scrutinized and he was then placed in one of four categories:

None

- proteinuria never detected.

Intermittent

- occasional traces of proteinuria noted in the past which were not simply associated with urinary tract infection.

Moderate

- proteinuria present at a level of ++ for 12 months at least.

Heavy

- persistent proteinuria of +++ or more.

Peripheral Neuropathy

Careful enquiry was made of any symptoms suggestive of peripheral neuropathy. Each symptom was explained in simple terms and patients were asked specifically about numbness, paraesthesiae, burning pains and muscle weakness in arms, legs or elsewhere. Where a patient said "Yes" to any of these symptoms then details were ascertained and the patient asked to grade this symptom as "mild", "moderate" or "severe." If a patient had one or more

positive responses then a neurological examination was carried out looking specifically for evidence of sensory loss, muscle wasting, absence of deep tendon reflexes, evidence of recent or old neuropathic ulceration. The decision as to whether or not a patient had symptomatic peripheral neuropathy was based on the clinical evidence. The criteria employed were the presence of one or more "severe" or two or more "mild / moderate" symptoms along with objective evidence that these symptoms were due to neuropathy. If a patient had no symptoms at all, then neurological examination was not carried out.

Autonomic Neuropathy

Careful enquiry was made of any symptoms suggestive of autonomic neuropathy. In each case the meaning of the symptom was explained, and, where a patient gave a positive response, further details were obtained to try to decide whether his symptom was likely to be due to autonomic neuropathy or not. Patients were asked specifically about whether, either at the present time or in the recent past, they had experienced postural hypotension, dysphagia, epigastric fullness, constipation, intermittent diarrhoea, hypoglycaemic unawareness, diminished sweating in the legs, gustatory sweating, bladder dysfunction (dribbling, poor stream, frequency, incontinence). For any positive responses the patient was asked to grade this symptom as "mild", "moderate" or "severe." If the patient had three or more "mild / moderate" symptoms then cardiovascular autonomic function tests were carried out using the methods described by Ewing et al (1978). These tests were carried out in the Department of Medicine at the Royal Infirmary, Edinburgh. More details of the tests used and the criteria for abnormality are given in the next chapter (pages 60 to 62). The criteria for the presence of symptomatic autonomic neuropathy were two or more "severe" or three or more "mild / moderate" symptoms along with at least one abnormal

cardiovascular autonomic function test.

Impotence

All the questions relating to sexual dysfunction were left till the end of the interview and until rapport was achieved with each man. The subject was first approached in a general way by asking if, since the onset of diabetes, he had ever experienced any difficulty with sex. Subsequent questions probed further until a clear picture was obtained. The criteria used for the presence or absence of erectile impotence were:

> ". . . complete inability to achieve and maintain an erection of sufficient rigidity and duration to allow vaginal penetration on all occasions of attempted intercourse during the past 6 months."

As this is a very strict set of criteria, one might expect that many men would fall into a category of "partial erectile dysfunction" which was intermediate between normality and the criteria set out above. It was found, however that there were so few men who fitted this category that, for the purposes of multivariate analyses they were included with the potent group.

For any man who did complain of erectile impotence, details were taken of the duration of impotence, the life circumstances which were present at the onset of erectile dysfunction, the presence or absence of spontaneous morning erections, whether the symptoms began suddenly or gradually, and whether it had been episodic or steadily progressive.

If impotence was absent then enquiry was made about whether the man had ever experienced temporary impotence in the past. If so, details were taken.

Libido

Each man was asked to say how he rated his interest in sex at the present time, compared with what he would consider should be normal. This was

recorded as normal, increased or decreased.

Ejaculation

Patients were asked if they were able to ejaculate in any circumstances and if so they were asked whether they considered their ejaculation to be normal or abnormal. If abnormal, then details were taken. This information was not used in the multivariate anlyses.

DATA HANDLING

Some of the data obtained from these semi-structured interviews were handled manually or were used for broad descriptive purposes only. In order to investigate which of these clinical features were independently associated with the presence of erectile impotence the technique of linear logistic modelling was employed. The rationale and methodology of this statistical technique has been described already (pages 1 to 8). The information from the semi-structured interview data sheets was firstly coded, then transferred to punch cards. Using the Edinburgh Regional Computing Centre's facilities the computer package BMDP was employed. Patient groups 1, 2 and 3 were compared using chi-squared tests or a one-way analysis of variance depending upon whether the variable concerned was qualitative or quantitative.

RESULTS

Comparison of the non-randomised groups (1 and 3) and the randomised group (2) were made. The differences between the groups are outlined below. There were few significant differences and they were such that the amalgamation of the grouped data would give valid results on diabetic impotence. The ages of the three groups were comparable with mean ± S.E.M. of groups 1, 2 and 3 being 43.4 ± 0.6 years, 46.1 ± 1.1 years and 43.7 ± 1.1 years respectively. The overall prevalence of impotence was 35%, 39% and 31%

respectively in the three groups. The only variables demonstrating significant differences between the groups (at the 5% level) were retinopathy with prevalences of 34%, 22% and 26% respectively and symptomatic peripheral neuropathy with prevalences of 23%, 13% and 14% in the three groups. All subsequent analyses were performed with the combined data from all three groups.

Of the 541 men interviewed, 190 (35%) were impotent (Table 3). The increasing prevalence of impotence with age is whown in Figure 2 and over the age range studied this relationship can be described adequately by a logistic curve. The prevalence is clearly greater among the diabetic men than among normal subjects.

Because age has such an obvious influence on the prevalence of impotence it is necessary to look at the effect of other variables on impotence within comparable age groups. Thus in Tables 4-10 three age groups were chosen to give adequate numbers in each group: 20-34 years; 35-49 years; 50-59 years.

The effect of duration of diabetes on the prevalence of impotence in insulin-dependent and noninsulin-dependent diabetics is shown in Tables 4 and 5. There was an increasing prevalence of impotence with increasing duration of diabetes in all age groups but no difference in prevalence was seen between the insulin-dependent and noninsulin-dependent groups. However, when analysed using the linear logistic regression model the effect of duration was found to be indirect. Duration of diabetes is associated with an increasing prevalence of many other aetiological factors such as microangiopathy and neuropathy and so its individual importance is not considered to be significant in the context of the analysis using the linear logistic model.

Using the linear logistic model five variables showed a significant

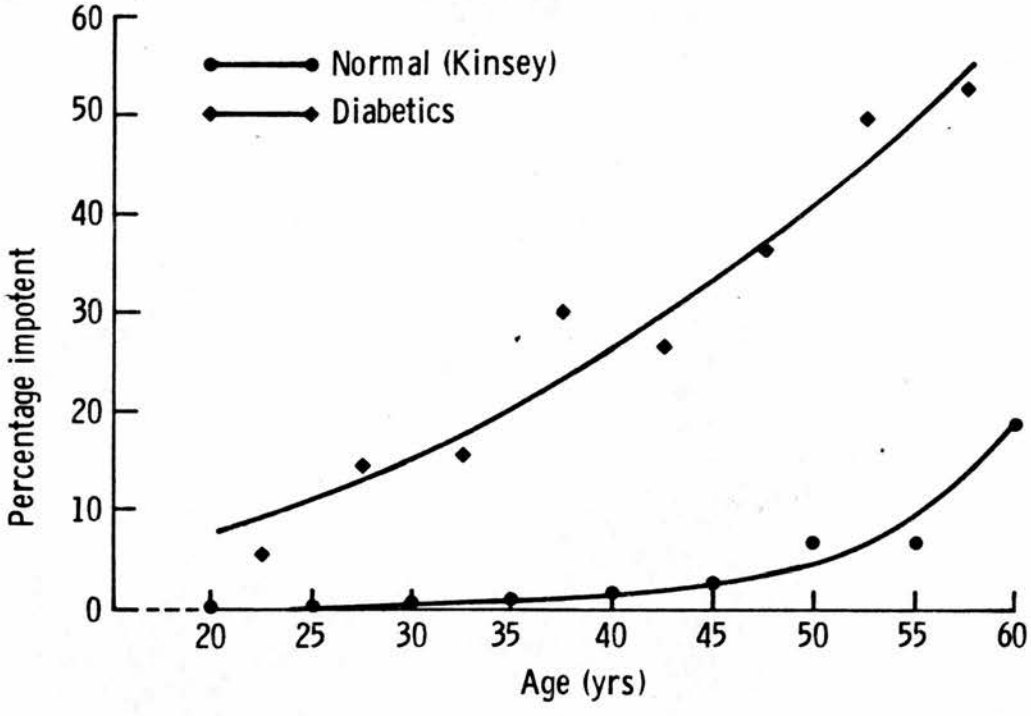


FIGURE 2. Relationship of impotence to age in diabetic and normal male subjects. The normal male data are derived from Kinsey et al (1948)

association with impotence: age ($p < 0.001$), treatment of diabetes with insulin or oral hypoglycaemic agent but not diet alone ($p < 0.001$), retinopathy ($p < 0.001$), symptomatic peripheral neuropathy ($p < 0.001$) and symptomatic autonomic neuropathy ($p < 0.005$).

In Table 6 it is seen that impotence is 2-3 times commoner among patients taking insulin or oral hypoglycaemic agents than among those on dietary restriction only. The reason for this difference is unclear but is apparently independent of age, duration of diabetes and level of diabetic control.

The effect of retinopathy on the prevalence of impotence is striking (Table 7). At all ages the prevalence of impotence rises sharply with increasing severity of retinopathy such that all men over the age of 50, with proliferative retinopathy were impotent.

The association of peripheral neuropathy and the presence of impotence is most marked among younger patients (Table 8). Thus only 7% of those under 35 years of age were impotent, if they had no evidence of symptomatic peripheral neuropathy. However, among those who did have evidence of peripheral neuropathy the prevalence rose to 44%.

The association between symptomatic autonomic neuropathy and erectile impotence is even closer (Table 9). Overall, 24/25 (96%) of men with other symptoms and signs of autonomic neuropathy were impotent.

Table 10 shows the relationship of nephropathy to impotence among diabetic men within these age groups. It can be seen that the prevalence of impotence rises sharply at all ages with increasing evidence of nephropathy. Thus, among men aged 35-49 years, for example, the prevalence of impotence among men with no clinical evidence of nephropathy is 28%. This rises to 100% in those men who show persistent heavy proteinuria. Because the trends in this

Table are so clear, it is surprising that the overall significance of nephropathy to the presence of impotence is so small ($p < 0.1$). The reason for this is that, as discussed before (pages 2 to 6) it is inappropriate to take a variable like "nephropathy" in isolation and then derive a "p-value" based on the data contained in Table 10. Patients with severe nephropathy have usually got evidence of severe retinopathy, peripheral neuropathy and autonomic neuropathy. Thus, when all these variables are used in the regression analysis it is found that nephropathy, per se, can be dropped from the analysis without affecting the regression.

The relationship between ischaemic heart disease and the prevalence of impotence is shown in Table 11. Although there is a suggestion, at least among men over 50 years of age that the presence of ischaemic heart disease is associated with impotence, the relationship is not strong.

Previous Episodes Of Transient Impotence

Transient impotence had occurred in 24 of the potent subjects, 8 during poor control, 4 during anxiety and 12 at times such as at diagnosis of diabetes (3 subjects), following excess alcohol (2 subjects) and during intercurrent unrelated illness such as myocardial infarction (7 subjects).

DISCUSSION

This study has confirmed that erectile impotence is considerably more prevalent among diabetics than in the general population, in all age groups. The overall prevalence (35%) is lower than any previous reports (Table 1). There may be several explanations for this. Firstly, no one over the age of 59 years was interviewed whereas most previous studies have included a significant number of subjects over the age of 60. Since the prevalence of impotence is higher among the elderly the overall prevalence will be increased by their inclusion. In fact,

the prevalence of impotence is so markedly affected by age that it is almost meaningless to quote or compare the overall prevalence rates between studies without taking the age distribution of the populations sampled into account.

Another reason for differences in the results seen in this study and previous reports is methods of case selections. A large number of patients were interviewed in this study. They were unselected as regards treatment, duration of diabetes or complications. The study was conducted over a nine month period to include less frequent clinic attenders. In addition a group of randomly selected patients was included. All of these aspects were employed so that the results obtained would be from a truly representative sample of patients.

A further difference between studies is with the definition of impotence used. In this study a rather strict definition of impotence was employed (see page 41). Since it is quite conceivable for a man to have significant sexual dysfunction and yet be "potent" by this definition, it is fair to assume that this study has not uncovered the whole spectrum of sexual dysfunction among this group of men. However, since one of the main purposes of the study was to identify which clinical features were associated with erectile impotence, it was felt that a strict and unambiguous definition was preferable.

The study has confirmed the view of Schoffling (1963) that impotence becomes more prevalent with increasing duration of diabetes. However the use of multivariate analysis would suggest that the effect of duration is indirect. The longer a patient has had diabetes the more likely he is to develop neuropathic and vascular complications which, in turn, show a close correlation with erectile impotence.

The significant association of impotence with diabetics on insulin or oral hypoglycaemic agents rather than diet alone is hard to explain, and differs from

two previous studies where impotence occurred equally in patients on all forms of therapy (Schoffling, 1960, Montenero and Donatone, 1962).

The results also suggest a strong association between impotence and the severity of microangiopathy. Although diabetics with severe retinopathy are more likely to have peripheral and autonomic neuropathy, in addition, the use of multiple regression analysis indicates that retinopathy has a significant association with impotence which is independent of neuropathy and other clinical factors. This is a new finding and was not seen in previous studies by Rubin and Babbott (1958) and Kolodny et al (1974) where retinopathy occurred with equal frequency in both potent and impotent diabetics.

It was not possible in this study to get an accurate assessment of previous glycaemic control and therefore one cannot make any confident statement about the effect of metabolic control on the development of impotence among diabetic men. However, since the development of retinopathy is regarded by many as being related to poor metabolic control (Tchobroutsky, 1978) this study provides indirect support for the notion that poor diabetic control may be associated with impotence.

Previous studies have shown that impotence is found in a high percentage of patients with peripheral neuropathy (Rundles, 1945; Martin, 1953) and with autonomic neuropathy (Ellenberg, 1971; Faerman et al, 1971). While these general trends have been confirmed in this study, it is pertinent to note that 127/436 (29%) of those without symptomatic peripheral neuropathy and 169/520 (33%) of those without symptomatic autonomic neuropathy were also impotent. This is still a much higher prevalence than would be expected in the non-diabetic population. The implication from these findings may be that impotence is the earliest manifestation of neuropathy and therefore antedates the clinical

expression of more overt neuropathic symptoms. Alternatively, the aetiology of impotence may be multifactorial with differing aetiologies among subgroups of impotent patients.

The independent effect of retinopathy on the prevalence of impotence suggests that, for some patients at least, microangiopathy may be the major "cause" for their impotence. Since any therapy for erectile impotence should be geared towards specific aetiological factors it is important to examine and investigate individual patients in more depth to elucidate the predominant causative factors in their case.

TABLE 3

Relationship of age to impotence in diabetic males

AGE RANGE (years)	TOTAL NO. DIABETICS	NO. DIABETICS IMPOTENT	% DIABETICS IMPOTENT
20 - 24	53	3	5.7
25 - 29	35	5	14.3
30 - 34	44	7	15.9
35 - 39	43	13	30.2
40 - 44	52	15	28.8
45 - 49	91	33	36.3
50 - 54	99	49	49.5
55 - 59	124	65	52.4
TOTALS	541	190	35.1

TABLE 4

Relationship of duration of diabetes to impotence in insulin-dependent diabetic men within three age groups

	Age (years)		
DURATION	20 - 34	35 - 49	50 - 59
0 - 4	2/40 (5%)	2/11 (18%)	3/9 (33%)
5 - 14	10/61 (16%)	15/40 (38%)	13/26 (50%)
15 - 29	3/24 (13%)	20/45 (44%)	26/33 (79%)
30+	—	6/13 (46%)	13/16 (81%)

TABLE 5

Relationship of duration of diabetes to impotence in noninsulin-dependent diabetic men within three age groups

	Age (years)		
DURATION	20–34	35–49	50–59
0 - 4	0/6	9/58 (16%)	26/75 (35%)
5 - 14	0/1	9/17 (53%)	28/56 (50%)
15 - 29	—	0/2	5/8 (63%)
30+	—	—	—

TABLE 6

Relationship of diabetic treatment to impotence in diabetic men within three age groups

	Age (years)		
TREATMENT	20 -34	35 - 49	50 - 59
Insulin	15/125 (12%)	43/109 (39%)	55/84 (65%)
Oral hypoglycaemic agents	0/3 (0%)	13/37 (35%)	43/77 (56%)
Diet alone	0/4 (0%)	5/40 (13%)	16/62 (26%)

$p < 0.001$ *

* See text for explanation.

TABLE 7

Relationship of retinopathy to impotence in diabetic men within three age groups

	Age (years)		
RETINOPATHY			
Grade	20 - 34	35 - 49	50 - 59
None	5/96 (5%)	29/120 (24%)	63/162 (39%)
Background	2/20 (10%)	12/35 (34%)	26/35 (74%)
Exudative	0/4 (0%)	6/13 (46%)	16/17 (94%)
Proliferative	8/12 (67%)	14/18 (78%)	9/9 (100%)

$p < 0.001$ *

* See text for explanation.

TABLE 8

Relationship of peripheral neuropathy to impotence in diabetic men within three age groups

	Age (years)		
PERIPHERAL NEUROPATHY	20 - 34	35 - 49	50 - 59
Absent	8/116 (7%)	44/151 (27%)	75/169 (44%)
Present	7/16 (44%)	20/35 (57%)	39/54 (72%)

$p < 0.001$ *

* See text for explanation.

TABLE 9

Relationship of autonomic neuropathy to impotence in diabetic men within three age groups

	Age (years)		
AUTONOMIC NEUROPATHY	20 - 34	35 - 49	50 - 59
Absent	11/127 (9%)	54/179 (30%)	104/213 (49%)
Present	4/5 (80%)	7/7 (100%)	10/10 (100%)

$p < 0.005$ *

* See text for explanation.

TABLE 10

Relationship of nephropathy to impotence in diabetic men within three age groups

	Age (years)		
NEPHROPATHY	20 - 34	35 - 49	50 - 59
None (0)	8/109 (7%)	43/155 (28%)	93/196 (47%)
Intermittent (0/+)	2/11 (18%)	8/18 (44%)	13/19 (68%)
Moderate (++)	4/10 (40%)	5/8 (63%)	4/4 (100%)
Heavy (+++)	1/2 (50%)	5/5 (100%)	4/4 (100%)

$p < 0.1$ *

* See text for explanation.

TABLE 11

Relationship of ischaemic heart disease to impotence in diabetic men within three age groups

		Age (years)	
ISCHAEMIC HEART DISEASE		20 - 34	35 - 49
Absent	15/132 (11%)	54/166 (33%)	83/174 (48%)
Present	0/0 (-%)	7/20 (35%)	31/49 (63%)

$p < 0.1$ *

* See text for explanation.

EVALUATION OF A SIMPLE URINARY FLOW RECORDING FOR THE ASSESSMENT OF DIABETIC IMPOTENCE

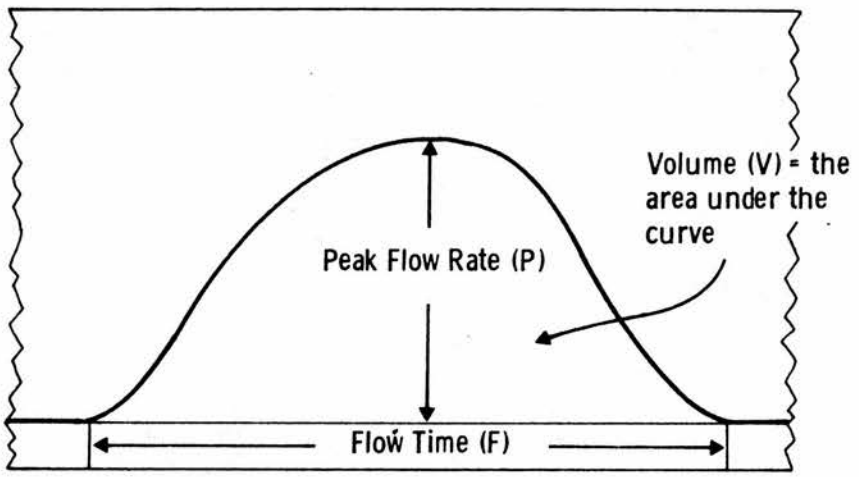
INTRODUCTION

As already discussed, the association of diabetic impotence with the presence of somatic and autonomic neuropathy is strong, although most of the evidence is indirect. In an attempt to look more directly at the nerves involved in penile erection some authors have evaluated bladder function in impotent diabetic men (Ellenberg, 1971; Faerman et al, 1972). Ellenberg used the technique of cystometry and found that 37 of 45 impotent diabetics had neurogenic bladder abnormalities compared with 3 of 30 potent diabetics. However, 38 of the impotent diabetics in Ellenberg's study had clinical evidence of neuropathy and are therefore not representative of a random sample of impotent diabetics. In my own study only 105 of 541 men had evidence of peripheral neuropathy, of whom 66 (35%) had clinical evidence of peripheral or autonomic neuropathy.

Investigation of urinary bladder dysfunction has been facilitated during the past decade by increasingly sophisticated techniques for bladder evaluation. Bradley et al (1975) have developed cystometry using gas as a filling medium and using detrusor reflex activating procedures. The commonest abnormalities seen with this technique are of detrusor areflexia and impaired sensation of bladder filling although occasionally detrusor hyper-reflexia has been found in patients with evidence of spinovascular disease. Sphincter electromyography (Bradley, 1976), urethral pressure profiles (Bradley et al, 1975) and electroencephalography (Bradley, 1977) have all been employed and show that the earliest abnormalities are impairment of peripheral visceral afferent pathways, followed later by detrusor reflex compensation.

Unfortunately all the above techniques are invasive and are therefore not applicable to large numbers of patients including asymptomatic and control subjects. The development of UROFLOWMETRY as an entirely non-invasive and simple procedure (Shoukry et al, 1975) has provided a potentially useful tool for examining bladder function in large numbers of subjects. In this procedure, the quantified measurement of urine flow (uroflowmetry) is done by having the patient void into a flowmeter. The flowmeter is a load cell mounted in the wall of a commode whose output is an instantaneous differential of the weight of the flow column and is therefore a measurement of urinary flow rate. A diagrammatic representation of the recording obtained in this procedure is shown in Figure 3. As shown the three main variables which can be measured are peak flow rate (P), total flow time (F) and volume of urine passed (V). From these it is possible to derive various indices of urinary function such as F/P, V/F, V/P and F/PxV. In diabetic patients the most common type of urine flow pattern observed is a low peak flow rate with a prolonged duration of flow (Bradley, 1980). Thus, the most useful measures would be P, F or F/P. However, since severe neurogenic bladder dysfunction is also associated with a reduced volume of micturition and a large residual volume (Ellenberg, 1971; Bradley, 1980) and since peak flow rate and flow time are at least partly related to the volume of urine passed, it might be more appropriate to derive an index of urinary flow which takes this into account (e.g. F/PxV).

The aims of this study were to assess the value of the technique of uroflowmetry in the assessment of erectile dysfunction among diabetic men. Firstly, it was hoped that the indices derived from uroflowmetry would help to pick out those diabetic men who had neuropathy as a main factor in their impotence. Secondly, we were interested to see how closely the indices derived



Possible measurements derived from mictiograph (see text)

(1) P = peak flow rate in ml per second
(2) F = flow time in seconds)
(3) V = total volume passed in ml
(4) F/P
(5) V/F
(6) V/P
(7) $\frac{F}{PXV}$

FIGURE 3 Normal urinary flow mictiograph.

from uroflowmetry would correlate with cardiovascular autonomic function tests.

PATIENTS AND METHODS

Fifty-one diabetic men whose potency had been determined in the epidemiological study were compared with 18 non-diabetic potent subjects who were staff members at the Royal Infirmary, Edinburgh. It was also hoped to compare the results of non-diabetic impotent men attending the sexual problems clinic at the Royal Infirmary but unfortunately only 4 of these subjects were obtained who were willing to take part and their data have not been included in the statistical analyses. The three comparison groups were therefore:

(A) 18 potent non-diabetics (mean age 42.3 years, range 24-60 years)

(B) 16 potent diabetics (mean age 38.9 years, range 24-53 years)

(C) 35 impotent diabetics (mean age 43.3 years, range 23-54 years)

ASSESSMENT OF CARDIOVASCULAR AUTONOMIC FUNCTION

In the past fifteen years a variety of simple non-invasive procedures have been developed to test cardiovascular reflex function. Much of the pioneering work in this field was carried out by Dr. David J. Ewing and co-workers in the University Department of Medicine at the Royal Infirmary in Edinburgh. The techniques employed and the criteria for normality are those described by Ewing and Clarke, 1982. Four tests were used on each diabetic subject. The first two (the Valsalva manoeuvre and the lying-to-standing heart rate response) assess cardiac parasympathetic function; the other two (measurement of postural hypotension and the blood pressure response to sustained handgrip) only show abnormal results when more widespread peripheral sympathetic damage is present.

(i) Valsalva Manoeuvre

During the strain of performing the Valsalva manoeuvre (forced expiration against resistance) there is normally tachycardia and peripheral vasoconstriction. After stopping the manoeuvre there is an overshoot rise in blood pressure and bradycardia. Heart rate changes give a reliable guide to the associated haemodynamic events (Ewing, 1978). The technique employed in this study involves the subject's blowing into a mouthpiece connected to a manometer held at 40 mm Hg pressure for fifteen seconds while a continuous ECG is recorded. The "Valsalva Ratio" is calculated by taking the longest R-R interval after the manoeuvre (reflecting the overshoot bradycardia) and dividing this by the shortest R-R interval (reflecting the tachycardia during strain). A Valsalva Ratio of 1.21 or greater is considered normal, 1.11 - 1.20 is borderline and 1.10 or less abnormal (Ewing et al, 1973).

(ii) Heart rate response to standing

The normal response to standing up quickly includes a rapid increase in heart rate, maximal at about the 15th beat after standing, with a subsequent relative bradycardia maximal at about the 30th beat. It has been shown that this reflex is mediated via the vagus nerve (Ewing et al, 1978) and that it can be quantified with a continuous ECG monitor by measuring the R-R interval at beat 30 and dividing this by the R-R interval at beat 15. The resulting "30/15 ratio" is normally greater than 1.03, while values of 1.01 - 1.03 are considered borderline while values less than 1.00 are abnormal (Ewing et al, 1978).

(iii) Blood pressure response to standing

Standing up quickly leads to pooling of blood in the legs, with a fall in blood pressure. However, this is normally corrected by vasoconstriction and tachycardia. Postural hypotension can be measured using a cuff sphygmomanometer, and a fall in systolic blood pressure of 30 mm Hg or more is

arbitrarily defined as abnormal (Clarke et al, 1979), 11-29 mm Hg as borderline and < 10 mm Hg as normal.

(iv) Blood pressure response to sustained handgrip

Sustained (isometric) muscular exercise normally causes an increase in systemic blood pressure (Ewing, 1978). A simple test, based on this reflex uses a handgrip dynamometer, standardised at 30% of the maximum voluntary contraction, with measurement of the blood pressure during handgrip (Ewing et al, 1974). A rise in diastolic blood pressure of 16 mm Hg or more is defined as normal, 11 to 15 mm Hg as borderline and 10 mm Hg or less as abnormal.

The results of these cardiovascular tests in the 51 diabetic men are shown in Tables 12 and 13.

ASSESSMENT OF URINARY FLOW PATTERNS

Urinary flow recordings were carried out in the Urological Day Bed Area of the Royal Infirmary, Edinburgh, using the Mictiograph machine. Each subject was tested on one occasion only. He was given water to drink until he felt a distinct desire to pass urine. Micturition was carried out in a private cubicle in the standing position.

The measurement of urinary flow time (F), peak flow rate (P), volume of urine passed (V) and the indices F/P and $F/PxVx10^{-3}$ are shown for potent non-diabetics in Table 14 and for the 51 diabetic men in Tables 15 and 16.

STATISTICAL ANALYSES

As will be seen from Figures 4 - 8, the data derived in this study are not normally distributed. Analyses were therefore performed using the following non-parametric tests. In Figures 4-7 the Mann-Whitney U test was applied to test significance levels between any two subgroups. In Figure 8 the Kendall Rank Correlation Coefficient was applied to test the association of the index

F/PxV against age. In Figure 9 the Kruskal-Wallis One-Way Analysis of Variance was applied to test whether there was a significant trend for the index F/PxV to rise with increasing cardiovascular autonomic dysfunction, irrespective of potency.

RESULTS

The results of the Cardiovascular autonomic function tests are shown in Tables 12 and 13. Any results which are borderline are marked with an asterisk (*) while those which are abnormal are marked thus (+). It can be seen that 11/16 (69%) potent diabetics have normal results in all four tests (Table 12) compared with only 7/35 (20%) impotent diabetics (Table 13). However there is a large range of abnormality among these 51 patients. In order to grade the overall severity of autonomic dysfunction the following system has been employed. For each test the subject gets a score of "0" for a normal result, "$\frac{1}{2}$" for a borderline result and "1" for an abnormal result. The score for all 4 tests is added up and this is presented in the extreme right hand column of Tables 12 and 13 as the OVERALL A.N. SCORE (where A.N. stands for Autonomic Neuropathy). Thus the range of severity is from "0", where all 4 tests are normal to "4" where all tests are abnormal.

The results which follow will firstly analyse the uroflowmetry data with respect to potency/impotency (Figures 4-8). Following this I will examine the correlation between the indices derived from uroflowmetry and the severity of autonomic dysfunction, irrespective of potency (Figure 9).

(A) Results of Uroflowmetry in Groups A to C

Peak urinary flow (P) rates were higher among potent subjects (Figure 4). The means were 32.4 mls/sec in Group A, 36.5 mls/sec in Group B and 22.2 mls/sec in Group C. There was no significant difference between the two potent

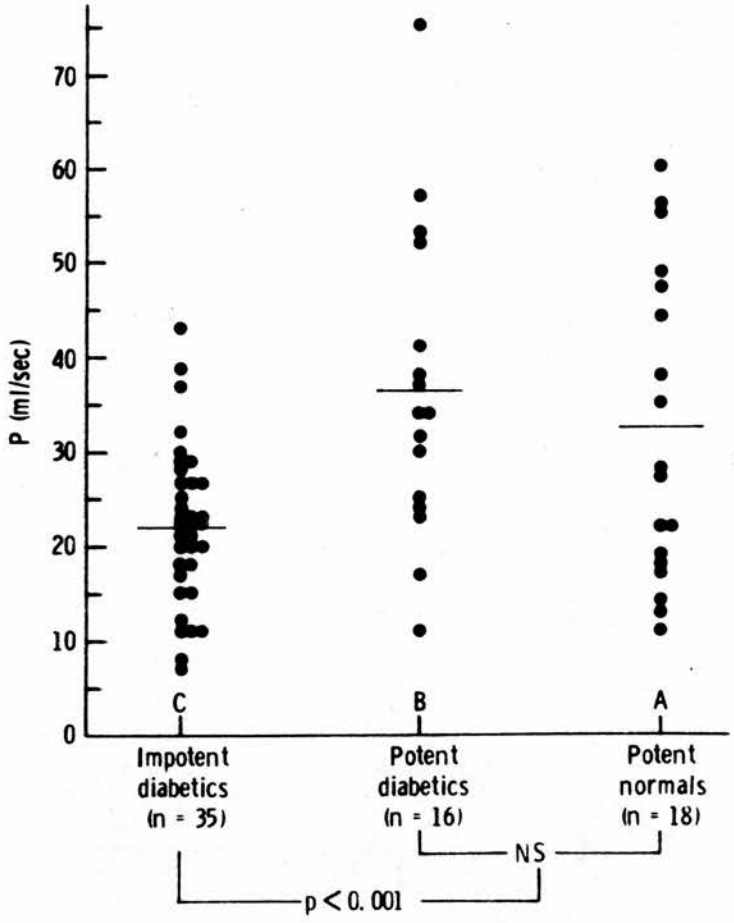


FIGURE 4 Distribution of peak urinary flow rate (P) among potent non-diabetics and potent and impotent diabetic subjects.

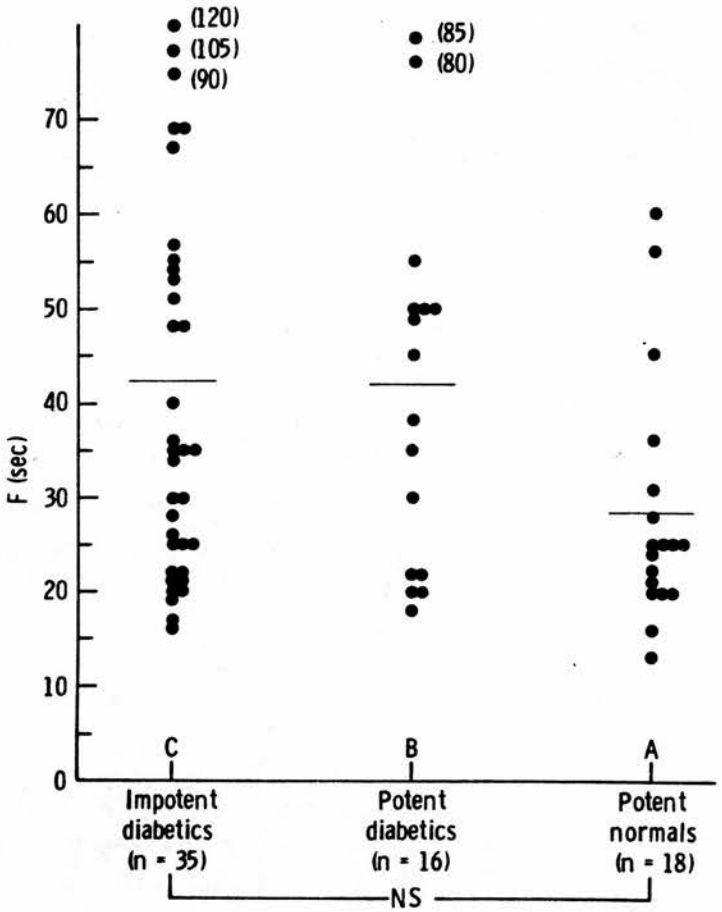


FIGURE 5 Distribution of urinary flow time (F) among potent non-diabetics and potent and impotent diabetic subjects.

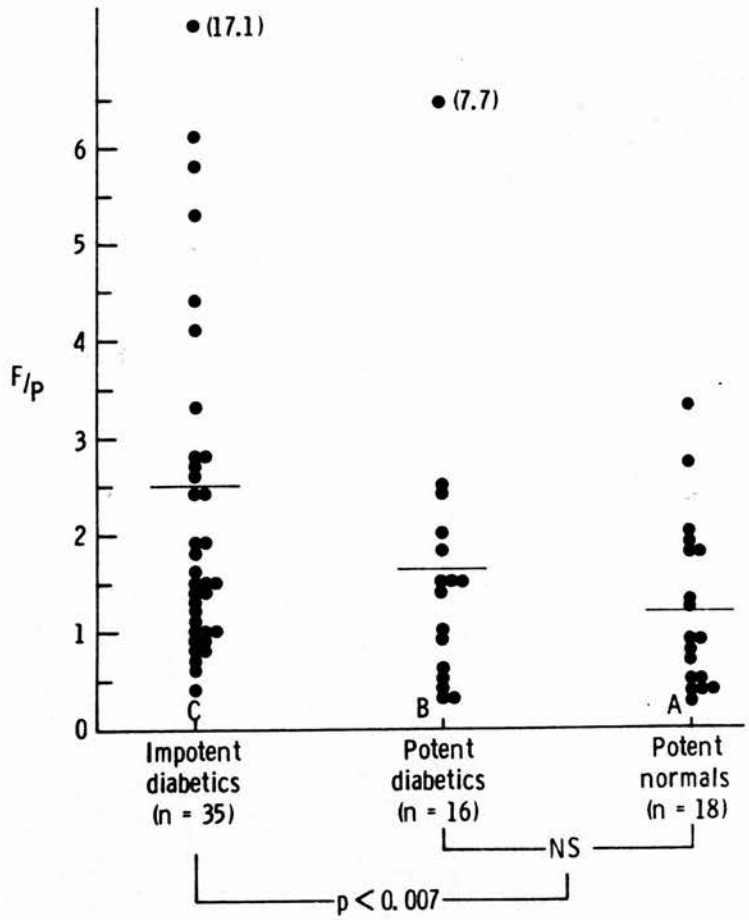


FIGURE 6 Distribution of the index: urinary flow time/peak urinary flow rate (F/P) among potent non-diabetics and potent and impotent diabetic subjects.

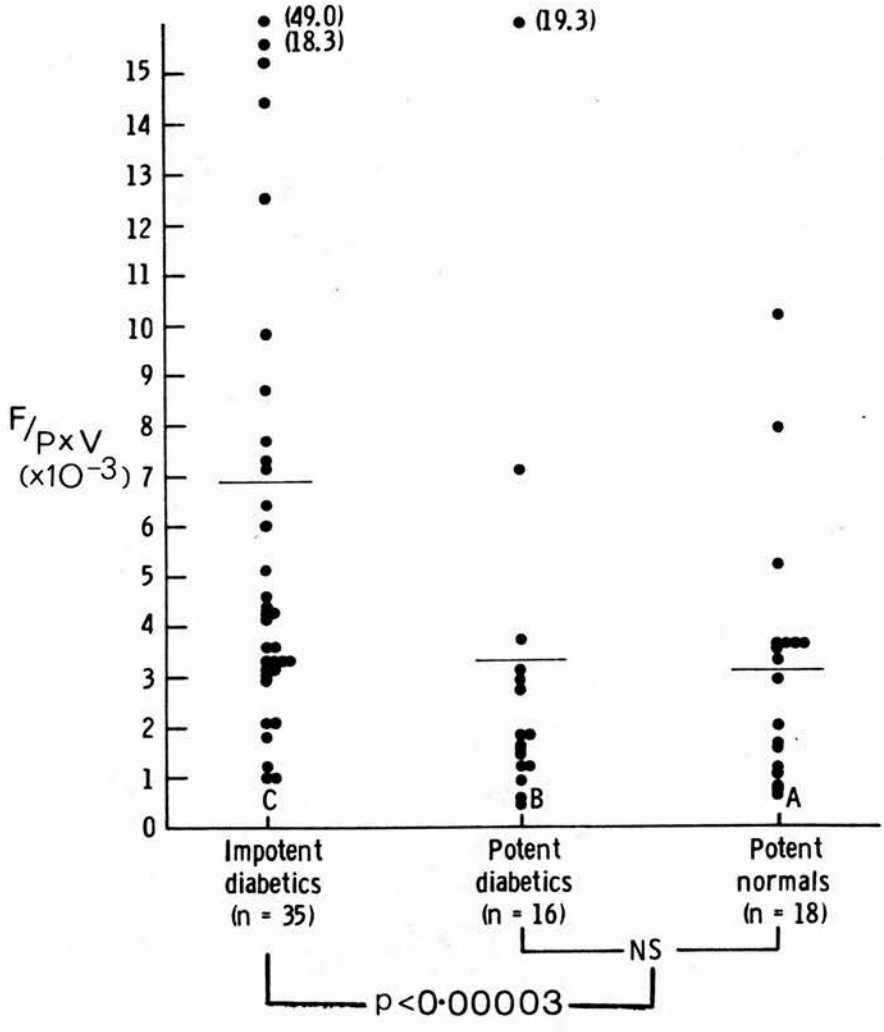


FIGURE 7 Distribution of the index: urinary flow time/ peak urinary flow rate X volume of urine passed (F/PXV) among potent non-diabetics and potent and impotent diabetic subjects.

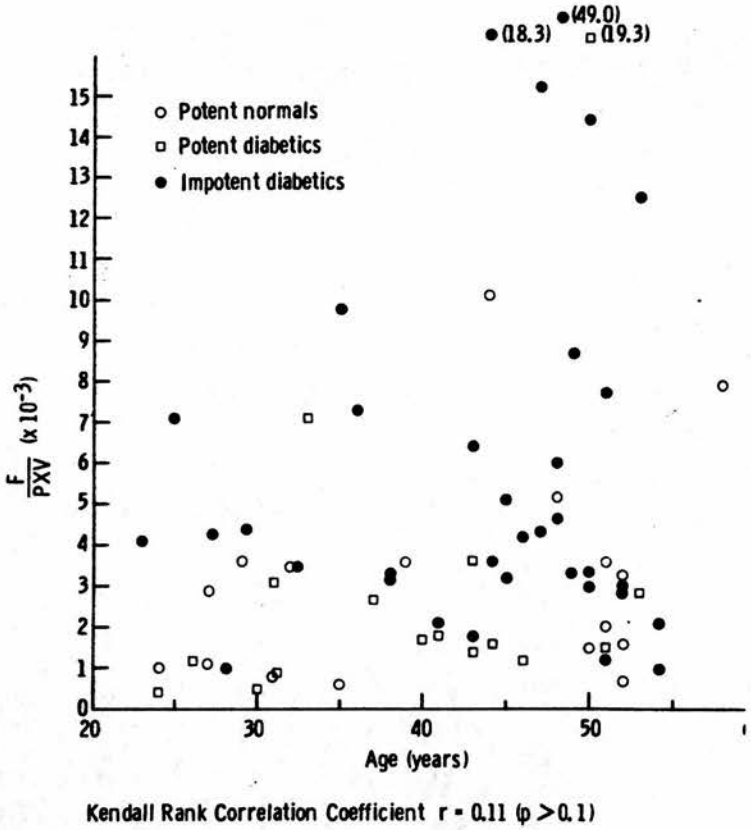


FIGURE 8 Correlation between the index F/PXV and age among diabetic and non-diabetic men.

groups A and B, but both of these groups had significantly higher peak flow rates than group C ($p < 0.001$). When looking at urinary flow time (Figure 5) although these seemed to be longer for the diabetic patients as a whole, none of the differences achieved statistical significance. However when urinary flow times were divided by peak flow rates for each individual (Figure 6) then the difference between potent men (groups A and B) and the impotent men becomes more obvious ($p < 0.007$). In order to try to separate the groups further, the index F/PxV was derived for each subject (Figure 7). Although this index did provide an even more confident separaton ($p < 0.00003$) the trends are essentially the same as those seen in Figure 6.

Although groups A, B and C had been matched closely for age, it is sensible to check that any differences in urinary flow measurements do not simply arise due to the effects of ageing (and consequent prostatic enlargement). Figure 8 shows the relationship of the index F/PxV to age in groups A, B and C. The correlation is very weak (Kendall Rank Correlation Coefficient $r = 0.11$, $p > 0.1$) and so the changes seen in Figures 4, 6 and 7 are more likely to be due to some other effect, independent of ageing.

(B) Correlation between indices derived from uroflowmetry and measurements of cardiovascular autonomic reflex function

There are several problems associated with categorising patients simply on the basis of being "potent" or "impotent." Firstly, this classification is subjective, and relies not only on the subject's honesty but also on his concept of normality. Secondly, by the definition employed, a man is either potent or impotent, there is no in between. In order to assess the role of autonomic nerve dysfunction in this situation it might be useful to compare the results of the established cardiovascular autonomic function tests with the indices derived

from uroflowmetry, since both of these are objective measurements which can be ranked from normality to abnormality. In Figure 9 the 51 diabetic patients have been regrouped (irrespective of potency) on the basis of their overall A.N. score. There were 18 patients whose tests were completely normal. A further 17 men had minimal abnormality with one or two borderline tests or one abnormal result (overall A.N. score $\frac{1}{2}$ - 1). The remaining patients were divided into those with an overall A.N. score of $1\frac{1}{2}$ - 2 (9 patients) and those with an overall A.N. score of $2\frac{1}{2}$ - 4 (7 patients). These four groups therefore exhibit increasingly severe cardiovascular autonomic dysfunction. From the first part of the analysis it was clear that the most discriminating index from uroflowmetry was $F/PxVx10^{-3}$ (Figure 7). Figure 9 shows the distribution of this index among these 4 groups of diabetic men. Although there is considerable scatter of the points, there is a trend for F/PxV to be lower in those patients showing little or no evidence of cardiovascular autonomic dysfunction and for this index to rise with increasingly severe autonomic neuropathy (Kruskal-Wallis One Way Analysis of Variance, $H = 8.45$; $p < 0.05$).

DISCUSSION

This study has confirmed that abnormalities of bladder function may occur among diabetic men. The most significant single measurement was the peak urinary flow rate (P) which was reduced in the impotent diabetic men. The evidence for a prolonged urinary flow time (F) was less convincing as a single measurement (Figure 5) but the index derived from flow time divided by peak flow (F/P) confirmed that both these features of bladder function are impaired in some diabetics, as suggested by Bradley (1980).

The fact that age matched potent diabetic men produced urinary flow patterns indistinguishable from the normal population suggests that these

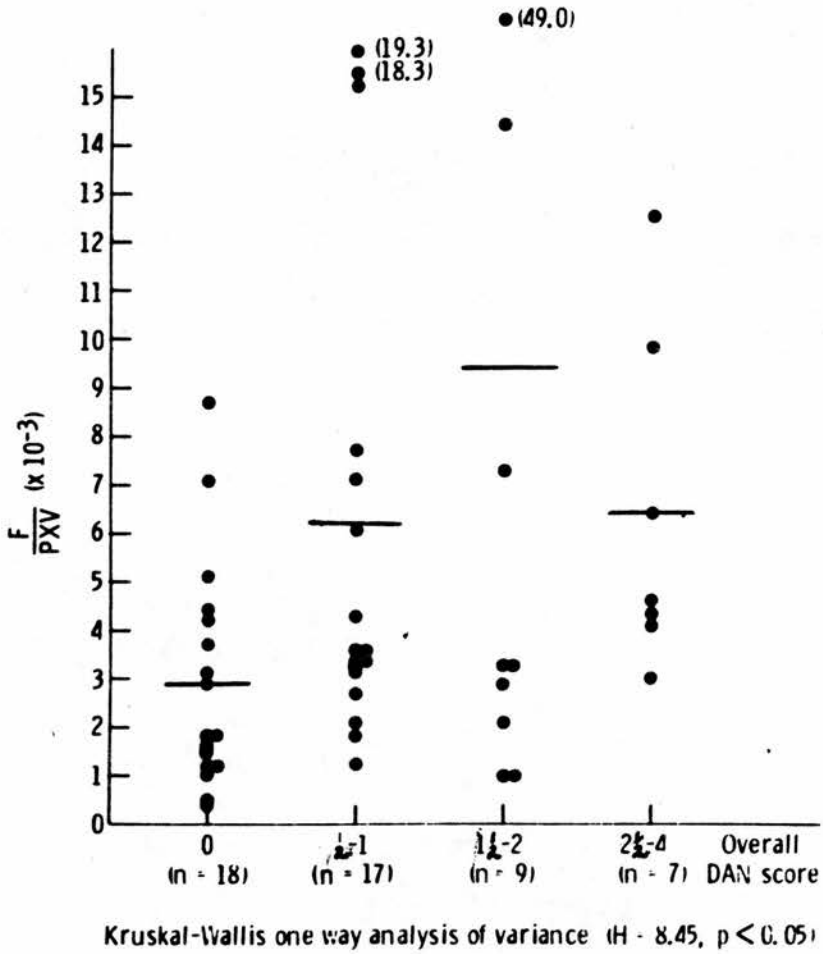


FIGURE 9 Distribution of the index F/PxV among diabetic men with differing degrees of cardiovascular autonomic dysfunction

abnormalities of bladder function are not caused by diabetes per se but rather by an associated autonomic neuropathy which occurs in some diabetics. In the absence of prostatic or urethral obstruction the abnormalities seen among the impotent diabetics of reduced flow rate and prolonged urinary flow time suggest motor denervation of the detrusor muscle of the bladder.

The index which best reflects these abnormalities of bladder function is F/PxV. The correlation between this index and abnormalities in cardiovascular A.N. tests (Figure 9) strengthens the idea that the changes seen in bladder function are partly due to autonomic neuropathy. This study therefore lends further support for the role of autonomic neuropathy in some cases of "diabetic impotence."

Although this study has shown that, as a group, impotent diabetic men have abnormal urinary flow patterns, the technique of uroflowmetry, as used here, is not precise enough to allow one to draw firm conclusions on individual patients. It is of interest however that of the 7 impotent diabetic men who had completely normal cardiovascular A.N. results, 4 (patients 21, 32, 34 and 40, Table 12) had abnormal urinary flow patterns. It may be that impotence is a very early symptom of autonomic neuropathy, in some cases, and that associated bladder abnormalities occur along with this, even before the cardiovascular autonomic nerves have been affected by neuropathy. Thus, although single urinary recordings among groups of patients in this cross-sectional study have not shown clear distinctions between the groups, it remains to be seen whether sequential urinary flow recordings in individual patients over a period of years would help to identify patients with developing pelvic autonomic neuropathy. Apart from the shortcomings of the technique of uroflowmetry used in this study one further explanation of the wide scatter of results could be that this is reflecting the

heterogeneity in the aetiology of impotence in diabetic men. Once again, sequential uroflowmetry data might help to distinguish those patients who have a major component of neuropathy in the aetiology of their impotence from those who do not.

Table 12

Results of Cardiovascular Autonomic Function Tests among 16 Potent Diabetic Men (Group B)

No	Patient	Age	Parasympathetic Function		Sympathetic Function		Overall A.N.Score
			Valsalva Ratio	30/15 Ratio	Postural change in systolic B.P. (mm Hg)	Handgrip response change in diastolic B.P. (mm Hg)	
1	DW	24	2.28	1.33	+15	+40	0
2	PE	26	1.28	1.22	-8	+42	0
3	VK	30	2.53	1.07	+8	+42	0
4	IT	31	1.21	0.96+	-26*	+20	1½
5	GP	31	1.33	1.15	+5	+35	0
6	WW	33	1.65	1.13	0	+35	0
7	AW	37	2.72	1.14	-20*	+31	½
8	MD	40	1.76	1.22	0	+20	0
9	SB	41	1.05+	1.10	0	+18	1
10	DC	43	2.54	1.58	+6	+12	0
11	RB	43	2.27	1.28	+10	+35	0
12	JF	44	1.40	1.13	-10	+24	0
13	DH	46	1.45	1.18	-10	+40	0
14	JM	50	1.44	1.00+	0	+15	1
15	JMcD	51	1.43	1.07	0	+20	0
16	CMcL	53	1.02+	1.03*	-15*	+25	2

* = borderline; + = abnormal; = see text for explanation

Table 13

Results of Cardiovascular Autonomic Function Tests among 35 Impotent Diabetic Men (Group C)

No	Patient	Age	Parasympathetic Function		Sympathetic Function		Overall A.N.Score
			Valsalva Ratio	30/15 Ratio	Postural change in systolic B.P. (mm Hg)	Handgrip response change in diastolic B.P. (mm Hg)	
17	RG	23	1.24	1.00+	-30+	+11*	2½
18	NC	25	1.70	1.00+	-5	+35	1
19	AB	27	1.33	1.00+	-10	+28	1
20	SW	28	1.43	1.00+	-56+	+22	2
21	DMcK	29	1.31	1.07	0	+25	0
22	DA	32	1.58	0.89+	0	+42	1
23	EL	35	1.00+	1.00+	-35+	+5+	4
24	DA	36	1.25	0.92+	-15*	+11*	2
25	KMcF	38	1.46	0.97+	-45+	+35	2
26	AS	38	-	1.00+	0	+45	1
27	JS	41	1.02+	1.00+	0	+20	2
28	AG	43	-	0.97+	-32+	+8+	3
29	OE	43	2.13	1.08	+25	+57	0
30	GG	44	1.95	1.07	-32+	+23	1
31	JM	44	1.24	1.03*	+5	+23	½
32	JL	45	1.78	1.14	-10	+40	0
33	AT	45	1.19*	0.97+	-25*	+20	2
34	MS	46	1.44	1.12	0	+60	0

Table 13 (cont.)

Results of Cardiovascular Autonomic Function Tests among 35 Impotent Diabetic Men (Group C)

No	Patient	Age	Parasympathetic Function		Sympathetic Function		Overall A.N.Score
			Valsalva Ratio	30/15 Ratio	Postural change in systolic B.P. (mm Hg)	Handgrip response change in diastolic B.P. (mm Hg)	
35	BG	47	1.33	1.06	0	+15*	½
36	FR	47	1.00+	1.00+	-5	+10+	3
37	JMcL	48	1.18*	0.93+	-40+	+10+	3½
38	DH	48	1.14*	0.97+	-28*	+17	2
39	LL	48	1.51	1.07	+10	+10	1
40	JG	49	1.55	1.06	0	+17	0
41	WS	49	1.25	1.06	-25*	+25	½
42	JM	50	1.08+	1.00+	-15*	+10+	3½
43	WP	50	1.04+	1.06	-15*	+20	1½
44	AB	50	1.12*	1.03*	-10	+22	1
45	EB	51	1.06+	1.09	-5	+27	1
46	WG	51	1.24	0.92+	-10	+20	1
47	JM	52	1.64	1.03*	+15	+30	½
48	EH	52	1.52	1.07	+10	+30	0
49	WL	53	1.00+	1.00+	+5	0+	3
50	RW	54	1.14*	1.11	-5	+18	½
51	RMcK	54	2.06	1.06	+5	+23	0

* = borderline; + = abnormal; = see text for explanation

Table 14

Results of Uroflowmetry among 18 Potent Non-diabetic Men (Group A)

Subject	Age	Flow Time (F)(sec)	Peak Flow (P)ml/sec	Volume (V)(ml)	F/P	F/PxV(10^{-3})
SB	24	21	47	450	0.4	1.0
JC	27	25	60	390	0.4	1.1
IS	27	22	27	285	0.8	2.9
DB	29	16	18	250	0.9	3.6
BF	31	20	56	450	0.4	0.8
FW	32	60	19	900	3.2	3.5
RC	35	13	49	425	0.3	0.6
DE	39	25	13	250	1.9	3.6
JB	44	36	11	325	3.3	10.1
PG	48	31	17	350	1.8	5.2
IJ	50	45	38	800	1.2	1.5
BW	51	20	44	225	0.5	2.0
DD	51	28	22	356	1.3	3.6
EE	52	56	28	600	2.0	3.3
AM	52	24	35	425	0.7	1.6
DC	52	25	55	700	0.5	0.7
LD	58	25	14	225	1.8	7.9
RP	60	20	22	250	0.9	3.6

Table 15

Results of Uroflowmetry among 16 Potent Diabetic Men (Group B)

No.	Subject	Age	Flow Time (F)(sec)	Peak Flow (P)ml/sec	Volume (V)(ml)	F/P	F/PxV(10^{-3})
1	DW	24	20	75	600	0.3	0.4
2	PE	26	35	38	800	0.9	1.2
3	VK	30	18	53	700	0.3	0.5
4	IT	31	50	52	1050	1.0	0.9
5	GP	31	49	24	650	2.0	3.1
6	WW	33	30	17	250	1.8	7.1
7	AW	37	80	32	950	2.5	2.7
8	MD	40	50	37	750	1.4	1.8
9	SB	41	45	30	850	1.5	1.8
10	DC	43	50	34	1050	1.5	1.4
11	RB	43	55	23	650	2.4	3.7
12	JF	44	22	34	400	0.6	1.6
13	DH	46	20	57	300	0.4	1.2
14	JM	50	85	11	400	7.7	19.3
15	JMcD	51	22	42	350	0.5	1.5
16	CMcL	53	38	25	525	1.5	2.9

Table 16

Results of Uroflowmetry among 35 Impotent Diabetic Men (Group C)

No.	Subject	Age	Flow Time (F)(sec)	Peak Flow (P)ml/sec	Volume (V)(ml)	F/P	F/PxV(10^{-3})
17	RG	23	30	21	350	1.4	4.1
18	NC	25	48	17	400	2.8	7.1
19	AB	27	35	18	450	1.9	4.3
20	SW	28	21	32	675	0.7	1.0
21	DMcK	29	25	25	225	1.0	4.4
22	DA	32	40	28	400	1.4	3.6
23	EL	35	22	15	150	1.5	9.8
24	DA	36	69	21	450	3.3	7.3
25	KMcF	38	26	20	400	1.3	3.3
26	AS	38	21	22	300	1.0	3.2
27	JS	41	53	30	860	1.8	2.1
28	AG	43	105	20	825	5.3	6.4
29	OE	43	28	37	425	0.8	1.8
30	GG	44	54	20	750	2.7	3.6
31	JM	44	22	8	150	2.8	18.3
32	JL	45	90	22	800	4.1	5.1
33	AT	45	35	24	450	1.5	3.2
34	MS	46	19	18	250	1.1	4.2
35	BG	47	67	11	400	6.1	15.2
36	FR	47	51	26.5	450	1.9	4.3

Table 16 (cont.)

Results of Uroflowmetry among 35 Impotent Diabetic Men (Group C)

No.	Subject	Age	Flow Time (F)(sec)	Peak Flow (P)ml/sec	Volume (V)(ml)	F/P	F/PxV(10^{-3})
37	JMcL	48	34	23	325	1.5	4.6
38	DH	48	120	7	350	17.1	49.0
39	LL	48	35	29	200	1.2	6.0
40	JG	49	36	15	275	2.4	8.7
41	WS	49	55	23	725	2.4	3.3
42	JM	50	30	29	350	1.0	3.0
43	WP	50	69	12	400	5.8	14.4
44	AB	50	20	27	225	0.7	3.3
45	EB	51	17	11	200	1.6	7.7
46	WG	51	25	43	500	0.6	1.2
47	JM	52	57	22	850	2.6	3.1
48	EH	52	20	23	300	0.9	2.9
49	WL	53	48	11	350	4.4	12.5
50	RW	54	25	27	450	0.9	2.1
51	RMcK	54	16	39	400	0.4	1.0

THE NATURAL HISTORY OF DIABETIC IMPOTENCE

INTRODUCTION

Very little is known about the factors leading to the development of erectile impotence in diabetes. Similarly, the prognosis for established impotence has not been clearly documented. Ellenberg (1971) suggested that it was an irreversible and progressive disorder with a poor prognosis in the vast majority of cases, although he produced no figures to back up this claim. In a prospective study over a five year period, Ewing et al (1980) examined the course of a small group of patients with symptoms of autonomic neuropathy. They found that deterioration and early death was common in those subjects with abnormal cardiovascular autonomic function tests, but that men with impotence as an isolated symptom and with normal autonomic function tests fared better than the rest.

The aim of the present study was to follow the progress of the large cohort of patients described previously (pages 35 to 57) in order to examine three areas. Firstly, what clinical festures among potent diabetic men are associated with the development of impotence? Secondly, what is the untreated natural history of diabetic impotence in terms of sexual dysfunction and the development of other diabetic complications? Finally, what factors affect the mortality in this group of patients?

PATIENTS AND METHODS

Of the original 541 men interviewed, 22 were untraceable while 36 had moved from the Edinburgh area. Six patients refused to be reinterviewed and a further 11 were considered unsuitable (5 for psychiatric reasons, 3 had cerebrovascular disease, 1 had sustained traumatic brain damage and 2 patients were no longer considered to have diabetes). This left 466 patients of whom 63 had died.

The remaining 403 men were re-interviewed. The mean time interval between first and second interview was 4 years 8 months (range 3 years 8 months to 6 years 2 months).

The questionnaire employed and the methods used were exactly the same as those described before (pages 36 to 42). Once again analysis of the data obtained was carried out using the facilities of the Regional Computing Centre. Statistical methods employed were mainly multivariate analyses involving the use of linear logistic models (Cox, 1970) fitted using the computer package Genstat.

RESULTS

The results will be presented in three parts: (i) Factors associated with the development of impotence. (ii) Progress of patients who were impotent originally and (iii) An analysis of deaths.

(i) Factors associated with the development of impotence

Of the 275 men who were potent at the original interview and were still available for study, 78 (28%) had become impotent. Using multivariate analysis, the factors present originally which were most strongly correlated with the development of impotence were age ($p < 0.0001$, Table 17, alcohol intake ($p < 0.0001$, Table 18), diabetic control ($p < 0.03$, Table 19), retinopathy ($p < 0.04$, Table 20) and intermittent claudication ($p < 0.05$, Table 21).

Examining these data in more detail it can be seen that the development of impotence was more than twice as common in men over 35 years of age than in those under 35 (Table 17). The effect of alcohol intake is even more striking (Table 18). While 22% of men who had mild alcohol intake (Grades 1 and 2) became impotent, this rose to over 50% in men who were heavy drinkers (Grades 3 and 4). The presence of poor diabetic control (Table 19) increased the

frequency of developing impotence from 22% to 33%. The association of retinopathy on the development of impotence was most marked in those men who had proliferative retinopathy at the original interview, where 60% have now become impotent (Table 20). Finally, although the numbers were smaller for intermittent claudication, it can be seen from Table 21 that the presence of intermittent claudication five years ago was associated with the development of impotence in 78% of cases.

(ii) Progress of patients who were impotent originally

Of the 128 men who were impotent at the original interview and were still available for study, only 11 (8.6%) have regained potency. Using multivariate analysis the factors present originally which were most strongly correlated with regained potency were young age ($p < 0.007$) and short duration of diabetes ($p < 0.01$). In addition, there were features present in several of these patients at the original interview which might have suggested a psychological cause, or other precipitating factors which were potentially reversible (Table 22). It is also worth noting that only 2 of these men had any other complications of diabetes. One man (patient 1) had background retinopathy and mild peripheral neuropathy, while another (patient 6) had mild peripheral neuropathy only.

The presence of impotence at the original interview was associated with the development of two other diabetic complications. of the 87 men who had impotence as an isolated diabetic complication, 14 have now developed symptomatic peripheral neuropathy, 5 have developed symptomatic autonomic neuropathy and a further 5 have developed both. In addition, of the 33 men who were impotent and had additional symptoms of peripheral neuropathy at the original interview, 6 have now developed symptomatic autonomic neuropathy in addition. Multivariate analysis has confirmed that the development of peripheral

neuropathy was associated with impotence ($p < 0.003$) and also with heavy alcohol intake ($p < 0.01$). Similarly, the factors present originally which were associated with the development of symptomatic autonomic neuropathy were poor diabetic control ($p < 0.004$), impotence ($p < 0.07$), duration of diabetes ($p < 0.04$) and peripheral neuropathy ($p < 0.07$).

(iii) Analysis of deaths

The mean age at death was 52.3 ± 9.0 years while the mean duration of diabetes was 16.7 ± 9.6 years.

The causes of death were ascertained in all 63 cases and are shown in Table 23. These were myocardial infarction (24 cases), sudden unexplained death (8 cases), chronic renal failure (6 cases), cardiac failure (6 cases), cerebro-vascular accident (5 cases), pneumonia (3 cases), pulmonary embolism (2 cases) and one case each of carcinoma of stomach, carcinoma of bronchus, hepatoma, cerebral tumour, carcinomatosis (from an unidentified primary tumour), septicaemia following amputation for gangrene, cirrhosis of the liver, ketoacidosis and hypoglycaemic coma.

Although 41 (65%) of the deaths were in men who had originally been impotent, impotence per se was not significantly associated with mortality when tested by multivariate analysis. Instead the most significant factors, present originally, which correlated with death during the subsequent five years were age ($p < 0.0001$), nephropathy ($p < 0.0001$), previous myocardial infarction ($p < 0.0001$), autonomic neuropathy ($p < 0.01$) and retinopathy ($p < 0.05$). Thus of the 41 impotent men who had died, only 6 (nos. 23 - 28, Table 23) had had impotence as an isolated complication of diabetes at the original interview. The remaining 35 impotent patients (nos. 29 - 63, Table 23) had had at least one other major complication of diabetes, when first interviewed.

This point is further illustrated by Table 24 which shows the distribution of causes of death in potent subjects (n = 22), those with impotence alone (n = 6) and those with impotence and other complications of diabetes (n = 35). It can be seen that the distribution is similar among potent men and those with impotence alone. The causes of death were somewhat different however among the impotent diabetics who had other diabetic complications. Five of the cases of chronic renal failure occurred in men who were known to have retinopathy and nephropathy. Also, 7 of the 8 cases of sudden death occurred in men who, along with impotence, had shown features of severe peripheral or autonomic neuropathy when first interviewed.

DISCUSSION

This study has defined, for the first time, the natural history of impotence in diabetic men. Of the 190 originally impotent patients, 41 had died during 5 years, 21 were unavailable or unsuitable and 128 were re-interviewed. Only 11 (9%) of those had regained potency. Even among those with "isolated" impotence at the outset (i.e. no micro/macro vascular disease or symptomatic neuropathy) only seven (16%) regained potency. Those recovering erectile function were significantly younger, had shorter duration of diabetes and often some psychological or organic factor had been present at initial interview which in retrospect was sufficient to account for temporary impotence. In the majority of cases, therefore, impotence developing in diabetic men is persistent. Impotence per se was also found to be significantly associated with the subsequent development of retinopathy and symptomatic peripheral and autonomic neuropathy but it did not confer an increased risk of mortality.

The original cross-sectional study demonstrated that established impotence was significantly associated with age, retinopathy and symptomatic peripheral

and autonomic neuropathy. Prospective studies, unlike cross-sectional data, can identify predictive as well as coexistent features with respect to a dependent variable such as impotence. They can not, however, determine whether such associations are causal. Nevertheless, on the basis of current pathological understanding it is reasonable to speculate that some of these significant associations might have aetiological roles in the development of impotence. Age, retinopathy, peripheral vascular disease, glycaemic control and alcohol intake at first interview were all associated with the development of impotence within 5 years. The association of advancing age and the development of impotence is not surprising and has been shown both in diabetics (Rubin and Babbott, 1958; Schoffling, 1960; Montenero and Donatone, 1962; Ellenberg, 1971; Faerman et al, 1972; Kolodny et al, 1974) and non-diabetics (Kinsey et al, 1948). The other findings are, however, new.

The relationships between retinopathy, peripheral vascular disease and impotence support the proposition that vascular as well as neuropathic features may play an important aetiological role in the pathogenesis of impotence, as suggested by others (Gaskell, 1971; Abelson, 1975; Ruzbarsky and Michal, 1977; Karacan et al, 1978, Michal, 1982). By contrast it may seem surprising that symptoms of peripheral and autonomic neuropathy were not predictive of the development of impotence since there is a well established association in cross-sectional studies. The probable explanation is that the majority of those with symptoms of peripheral neuropathy (63%) or autonomic neuropathy (95%) at review were already impotent at the original interview. This conclusion is also supported by the observed tendency for neuropathy and impotence to develop concurrently during the follow-up period. Thus impotence tends to come first. This study would therefore support a mixed vascular (micro and macro) and

neuropathic aetiology for impotence in diabetic men.

The associations which perhaps have the greatest interest with respect to potential management are the relations with glycaemia and alcohol. It is reasonable to imagine that the effect of poor glycaemic control on the development of impotence might be exerted through acceleration of diabetic complications. The association is relatively weak, however, although this may be due to the imprecise method of documenting glycaemic control. A strong link has been found with drinking, however, even though the documentation of alcohol consumption is notoriously inaccurate. In this study alcohol appears to have a uniform effect in increasing the prevalence of impotence irrespective of the preceding or parallel development of other diabetic complications. It remains to be seen whether close attention to diabetic control and alcohol abstinence will have a beneficial effect in established cases of impotence in diabetics.

This study has also clarified the prognosis of established diabetic impotence. It is worth re-emphasizing that almost 70% of patients who had impotence as an isolated complication of diabetes have remained with impotence alone, or, in a few cases, have regained potency during five years of follow-up. Relatively few of these patients have progressed to show other features of neuropathic or microvascular damage or have died. This should be contrasted with the very gloomy outlook for impotent diabetics who have evidence of retinopathy, nephropathy or autonomic neuropathy. Very few of these subjects regained potency spontaneously during five years of follow-up and almost half died. Care should be taken, therefore, in selecting suitable patients for treatment. It seems likely that the chances of success will be higher in patients who have impotence as an isolated complication of diabetes.

The aetiological factors which were found to be correlated with mortality

in this study were age, retinopathy, nephropathy and autonomic neuropathy. Deckert et al (1967) showed that retinopathy carries a poor prognosis in diabetes while Watkins et al (1972) described proteinuria as carrying a poor outlook. The observations in the present study regarding autonomic neuropathy confirm the findings of Ewing et al (1980). Impotence alone is not associated with an excessmortality although when associated with other features of autonomic neuropathy, the outlook is very poor. The fact that episodes of unexplained "sudden death" were common among these subjects provided further speculation. Ewing et al (1976) have postulated that these deaths may be directly attributable to abnormal cardiovascular reflexes and others (Page and Watkins, 1978) have supported this idea by demonstrating episodes of cardio-respiratory arrests in such subjects.

Overall this study suggests that the term "diabetic impotence" describes a group of conditions which may have quite different aetiologies and natural histories. The prognosis with regard to continuing sexual dysfunction, progression of other diabetic complications and mortality are determined largely by other related factors which can be easily determined by taking a careful history and examination, supplemented by a few simple tests.

TABLE 17

Relation of AGE to the development of impotence among 275 diabetic men, potent at first interview.

Age (years)	Still potent No (%)	Now impotent No (%)
< 35	76 (86%)	12 (14%)
35 - 49	64 (63%)	37 (37%)
50 - 59	57 (66%)	29 (34%)
TOTALS	197 (72%)	78 (28%)

$p < 0.0001$

TABLE 18

Relation of ALCOHOL INTAKE to the development of impotence among 275 diabetic men, potent at first interview.

Alcohol Intake	Still potent No (%)	Now impotent No (%)
Mild (Grades 1 and 2)	170 (78%)	47 (22%)
Heavy (Grades 3 and 4)	27 (47%)	31 (53%)
TOTALS	197 (72%)	78 (28%)

$p < 0.0001$

TABLE 19

Relation of DIABETIC CONTROL to the development of impotence among 275 diabetic men, potent at first interview.

Diabetic control	Still potent	Now impotent
Good	80 (78%)	22 (22%)
Fair	78 (68%)	37 (32%)
Bad	39 (67%)	19 (33%)
TOTALS	197 (72%)	78 (28%)

$p < 0.03$

TABLE 20

Relation of RETINOPATHY to the development of impotence among 275 diabetic men, potent at first interview.

Retinopathy	Still potent No (%)	Now impotent No (%)
None	163 (73%)	60 (27%)
Background	26 (67%)	13 (33%)
Exudative	6 (75%)	2 (25%)
Proliferative	2 (40%)	3 (60%)
TOTALS	197 (72%)	78 (28%)

$p < 0.04$

TABLE 21

Relation of INTERMITTENT CLAUDICATION to the development of impotence among 275 diabetic men, potent at first interview.

Intermittent claudication	Still potent No (%)	Now impotent No (%)
Absent	195 (73%)	71 (27%)
Present	2 (22%)	7 (78%)
TOTALS	197 (72%)	78 (28%)

p . 0.05

TABLE 22

Details of 11 patients who regained erectile potency during five years follow-up.

Patient	Age (years)	Duration of Diabetes	Unusual features at original interview
1	45	12 years	Marital problems.
2	49	4 years	Taking phenoxybenzamine.
3	25	6 months	Partial impotence for less than 1 month. Anxiety at diagnosis of diabetes.
4	43	18 years	Partial impotence for 10 months.
5	24	7 years	Found to be hypogonadal and responded to testosterone.
6	50	2 months	Partial impotence following the death of his wife.
7	48	2 months	Sudden deterioration in metabolic control prior to initial interview. Potency recovered after conversion to insulin.
8	30	8 years	Psychological features marked. Claimed to have become completely impotent since the diagnosis of diabetes at the age of 22.
9	37	15 years	Problems with his second marriage. "Performance anxiety" was a marked feature.

TABLE 22 (cont.)

Details of 11 patients who regained erectile potency during five years follow-up.

Patient	Age (years)	Duration of Diabetes	Unusual features at original interview
10	58	1 year	His main complaint was of a reduced facility in obtaining an erection.
11	49	5 months	The main problem was of ill-sustained erections and premature ejaculations.

TABLE 23

Details of 63 patients known to have died during five years of follow-up

Patient	Potency at original interview	Age at death (years)	Duration of diabetes at death (years)	Retinopathy	Peripheral Neuropathy	Autonomic Neuropathy	Cause of death
1	P	40	13	0	0	0	Chronic Renal Failure
2	P	51	29	+	0	0	Myocardial Infarction
3	P	51	34	+	0	0	Myocardial Infarction
4	P	52	15	0	0	0	Cardiac arrest during ketoacidosis
5	P	62	4	0	+	0	Myocardial Infarction
6	P	61	17	0	+	0	Cerebro-vascular Accident
7	P	58	4	0	+	0	Cerebro-vascular Accident 3 days after pancreatectomy
8	P	56	10	0	0	0	Myocardial Infarction

TABLE 36 (cont.)

Details of 63 patients known to have died during five years of follow-up

Patient	Potency at original interview	Age at death (years)	Duration of diabetes at death (years)	Retinopathy	Peripheral Neuropathy	Autonomic Neuropathy	Cause of death
9	P	59	31	0	0	0	Pulmonary embolus and advanced lymphoma
10	P	38	23	+	0	0	Myocardial Infarction
11	P	41	15	0	0	0	Cerebral Tumour
12	P	58	12	0	0	0	Sudden death at home
13	P	49	7	0	0	0	Cardiac Failure
14	P	25	16	0	0	0	Cardiac Failure
15	P	58	4	0	0	0	Cardiac Failure
16	P	51	10	0	+	0	Mycardial Infarction
17	P	59	14	0	+	0	Mycardial Infarction

TABLE 25 (Cont.)

Details of 63 patients known to have died during five years of follow-up

Patient	Potency at original interview	Age at death (years)	Duration of diabetes at death (years)	Retinopathy	Peripheral Neuropathy	Autonomic Neuropathy	Cause of death
18	P	54	5	0	+	0	Myocardial Infarction
19	P	60	7	0	+	0	Septicaemia after mid-thigh amputation for gangrene
20	P	53	9	0	0	0	Carcinomatosis (un-identified primary)
21	P	49	3	0	0	0	Cardiac Failure
22	P	59	14	+	0	0	Myocardial Infarction
23	I	53	22	0	0	0	Carcinoma of stomach
24	I	60	4	0	0	0	Myocardial Infarction
25	I	57	9	0	0	0	Hypoglycaemic coma

Details of 63 patients known to have died during five years of follow-up

Patient	Potency at original interview	Age at death (years)	Duration of diabetes at death (years)	Retinopathy	Peripheral Neuropathy	Autonomic Neuropathy	Cause of death
26	I	57	2	0	0	0	Myocardial Infarction
27	I	54	1	0	0	0	Myocardial Infarction
28	I	59	8	0	0	0	Myocardial Infarction
29	I	32	28	+	0	0	Pneumonia
30	I	62	39	+	0	0	Myocardial Infarction
31	I	57	21	+	0	0	Cerebro-vascular Accident
32	I	52	16	+	0	0	Chronic Renal Failure
33	I	42	13	+	0	0	Left Ventricular Failure

Details of 63 patients known to have died during five years of follow-up

Patient	Potency at original interview	Age at death (years)	Duration of diabetes at death (years)	Retinopathy	Peripheral Neuropathy	Autonomic Neuropathy	Cause of death
34	I	60	24	+	0	0	Myocardial Infarction
35	I	55	26	+	0	0	Cerebro-vascular Accident
36	I	56	16	0	+	0	Myocardial Infarction
37	I	60	18	0	+	0	Acute on chronic bronchitis
38	I	57	10	0	+	0	Hepatoma
39	I	61	13	0	+	0	Carcinoma of bronchus
40	I	57	7	0	+	0	Cirrhosis of liver
41	I	52	23	+	+	0	Left ventricular failure

Details of 63 patients known to have died during five years of follow-up

Patient	Potency at original interview	Age at death (years)	Duration of diabetes at death (years)	Retinopathy	Peripheral Neuropathy	Autonomic Neuropathy	Cause of death
42	I	59	10	+	+	0	Sudden death
43	I	59	18	+	+	0	Sudden death
44	I	40	31	+	+	0	Pulmonary embolus, 4 days after transurethral prostatectomy
45	I	54	23	+	+	0	Myocardial Infarction
46	I	53	22	+	+	0	Myocardial Infarction
47	I	52	19	+	+	0	Chronic Renal Failure
48	I	59	15	+	+	0	Bronchopneumonia
49	I	30	16	+	+	+	Chronic Renal Failure

TABLE 3b (cont.)

Details of 63 patients known to have died during five years of follow-up

Patient	Potency at original interview	Age at death (years)	Duration of diabetes at death (years)	Retinopathy	Peripheral Neuropathy	Autonomic Neuropathy	Cause of death
50	I	39	20	+	+	+	Cerebro-vascular Accident
51	I	45	18	+	+	+	Chronic Renal Failure
52	I	56	27	+	+	+	Myocardial Infarction, 2 days after below-knee amputation.
53	I	62	45	+	+	+	Myocardial Infarction
54	I	57	26	+	+	+	Chronic Renal Failure
55	I	53	24	+	+	+	Myocardial Infarction
56	I	60	15	+	+	+	Myocardial Infarction
57	I	62	22	+	+	+	Myocardial Infarction

TABLE 3c (cont.)

Details of 63 patients known to have died during five years of follow-up

Patient	Potency at original interview	Age at death (years)	Duration of diabetes at death (years)	Retinopathy	Peripheral Neuropathy	Autonomic Neuropathy	Cause of death
58	I	57	14	+	+	+	Myocardial Infarction
59	I	57	8	+	+	+	Myocardial Infarction
60	I	41	13	+	+	+	Sudden death
61	I	38	13	+	+	+	Sudden death
62	I	31	16	+	+	+	Sudden death
63	I	42	37	+	+	+	Sudden death

TABLE 24

Distribution of causes of death among men who were originally potent (n = 22), had impotence alone (n = 6) and had impotence plus complications (n = 35).

CAUSE OF DEATH	Potent (n=22)	Impotence alone (n=6)	Impotence plus complications (n=35)	Totals
Myocardial Infarction	9	4	11	24
"Sudden death"	1	0	7	8
Chronic renal failure	1	0	5	6
Cardiac failure	4	0	2	6
Cerebrovascular Accident	2	0	3	5
Other causes	5	2	7	14

CONCLUSIONS

"Diabetic impotence" is a complex condition which has received scant attention from physicians in the past partly because of embarrassment and ignorance and a belief that it is progressive and untreatable. In trying to unravel the complexities and reach a clearer understanding of the condition I have attempted with the help of collaborating colleagues to follow a logical natural progression. In the cross-sectional epidemiology, I have described the size of the problem. Almost a quarter of diabetic men under the age of 50 years have erectile impotence and this figure rises to over 50% in men over 50 years of age. Given that the problem is large, then it is important to elicit exactly what it is that these men are complaining of. Patients often find it difficult to describe sexual dysfunction, due partly to embarrassment and partly to a lack of precise vocabulary. The term "impotence" is commonly used by these patients but as shown by the work of Fairburn et al (Appendix C), when time and privacy allow a more detailed interview one can uncover a much wider clinical spectrum of sexual dysfunction which makes the understanding and management of individual cases much easier. There is ample evidence from the literature and from the results of my own studies in this thesis that such detailed clinical histories from impotent diabetic men are rarely obtained. Much of the misery for the patient and his sexual partner, stems from ignorance. Whatever else one can achieve in the management of diabetic impotence it should certainly be possible to improve this aspect of their care.

In trying to understand the aetiology of diabetic impotence, this thesis has provided evidence, both from epidemiological studies and from clinical investigation that a variety of factors are involved in different cases. The evidence that neuropathic damage plays a major role in some impotent diabetic

men is convincing. Both symptomatic peripheral and autonomic neuropathy were strongly correlated with the presence of impotence in the cross-sectional study. It is interesting that neither of these factors were shown to be associated with the development of impotence de novo among potent diabetic men followed prospectively. I think that the likely explanation of this apparent anomaly is that the nerve supply to the genitals is probably more vulnerable to damage than other peripheral and autonomic fibres. Thus, by the time these men show evidence of symptomatic peripheral or autonomic neuropathy, many will already have developed impotence. The data on associated bladder function described in pages 58 to 74 certainly support the idea that pelvic autonomic nerve damage plays a major role in some cases of diabetic impotence.

The role of vascular pathology in diabetic impotence has been largely ignored until recently. Both of the epidemiological studies in this thesis have suggested that microvascular disease (indicated by the presence of retinopathy) and macrovascular disease (indicated by the presence of ischaemic heart disease and intermittent claudication) play a major role in the development of diabetic impotence. The importance of an adequate vascular supply was also shown by investigations by Bancroft et al (Appendix B) which also demonstrated how delicate and vulnerable are the neuroregulatory controls on this vascular supply.

Psychological factors have often been played down in diabetic impotence which has been regarded by many as a good example of purely organic impotence. From the detailed clinical descriptions outlined by Fairburn et al, it is clear that this is not the case. Psychological factors are certainly the precipitating cause of impotence in some cases, as exemplified by some of the cases in Table 22. In addition the morbidity associated with diabetic impotence is largely determined by the psychological reactions of the patient and his sexual

partner.

With improved understanding of the size of the problem and of the aetiological factors which may lead to its development it should be possible to design more appropriate treatment programmes for these patients. These should also, however, take into account a knowledge of the natural history of the untreated condition. I have shown that the chances of spontaneously regaining potency are low and are related to the presence of psychological factors or reversible organic disorders which will respond to treatment (see Table 22). The outlook is also poor for men who have developed impotence in association with other major diabetic complications. However, this still leaves a large number of patients who have impotence as an isolated complication of diabetes. Almost 80% of this group remain in status quo during five years of follow-up. I would suggest that this is a group of impotent diabetics where attempts at treatment could be most usefully directed.

Although I have not attempted any therapeutic intervention in the studies outlined in this thesis it should be possible to design more appropriate treatment programmes for individual cases using the understanding which has been gained.

When a diabetic patient complains of "impotence" it is essential to take a detailed history to determine exactly what he means by this. The history should separate aspects of libido, erectile function and ejaculatory disturbance. The speed of onset and the presence of precipitating factors should be determined. These include changes in life circumstances such as worries regarding finance, employment or marital stress as well as the influence of pharmacological precipitants such as drugs (notably phenothiazines and antidepressant agents) and alcohol. Enquiry must be made regarding the reaction of the patient and his partner to the condition and their expectations of treatment. A knowledge of

the past sexual history is also helpful in understanding how the present sexual difficulty has developed.

Details of the patient's diabetic control should be obtained along with an assessment of the severity of other diabetic complications.

Investigations should be kept to a minimum and should be undertaken early in the course of management. The tendency to over investigate and to prolong this aspect may have a deleterious effect on the patient's response to treatment. It should be made clear to him that one is unlikely to stumble on a simple physical cause for his impotence which can be easily remedied and that these investigations merely form one aspect of his overall assessment. Despite these reservations I believe that some investigations will prove helpful in deciding appropriate treatment. Although endocrine distrubances play a very minor role in most cases of diabetic impotence it is probably worth excluding hypogonadism (by measuring gonadotrophins and testosterone), hypothyroidism (by measuring thyroid function tests) and hyperprolactinaemia (by measuring prolactin). These investigations are simple to perform in most centres and may occasionally provide an easy form of treatment (for example patient no. 5, Table 22). Other useful investigations include cardiovascular autonomic function tests (as described by Ewing et al, 1976). While the normality of these tests does not refute an organic component to the impotence, when these tests are shown to be abnormal this has serious implications for the likely prognosis of the condition.

More specific investigations might include those described by Bancroft et al (Appendix B). While these are sophisticated and could not be carried out in every medical centre they remain a useful investigation which may well help to distinguish between the importance of psychological and organic factors in individual cases of impotence.

Because of the heterogeneity of the aetiology of diabetic impotence described above it is difficult to speculate on what course of management should be employed following the results of all these findings. The management must be determined by what has been found in an individual case. Some points remain clear, however. In all cases it sould be possible to relieve some of the anxiety and misery associated with diabetic impotence by explaining both to the patient and his partner what the cause of the impotence is, in his case, and what the likely prognosis will be. Although isolated reports of the beneficial effects of more formal psycho-sexual counselling have been made (Renshaw, 1975) there is a need for a large controlled clinical trial of this form of treatment. Similarly with more physical approaches to treatment such as reconstructive vascular surgery and prosthetic penile implantation, there is a need for more critical assessment and more stringent inclusion criteria and post-operative follow-up.

Inevitably with a study of this magnitude there remain several areas where one's understanding is still incomplete and where further investigations need to be carried out. In particular I feel that there is still no satisfactory and simple way of determining which patients may respond best to any particular form of treatment. However, the studies which I have described in this thesis have certainly clarified my own understanding of erectile impotence in diabetic men. I am currently continuing my studies of this disorder by looking at the effect of various forms of treatment. It is my sincere hope that this thesis, and other published work derived from these data, will stimulate others to look into this distressing clinical condition with more understanding so that the dismal outlook for these men may be improved in years to come.

APPENDIX A

Data collection sheets for semi-structured interviews used in cross-sectional and prospective epidemiological studies of diabetic impotence

DIABETIC IMPOTENCE STUDY D.O.P.D. No._____ Study No._____

DATE _____

NAME _____ Coding

ADDRESS _____

_____

_____

HEIGHT _____ WEIGHT _____ STANDARD WT. ____

AGE _____ years AGE AT ONSET OF DIABETES _____ years.

MARITAL STATUS Married / Single / Divorced / Separated / Widowed / Other

DIABETIC TREATMENT Insulin * / O.H.A. * / Diet alone.

*Specify _____

OTHER DRUG THERAPY _____

_____

_____

OTHER ILLNESSES

		Details, if "YES"
Angina	YES / NO	_____
		_____
Myocardial Infarction	YES / NO	_____
		_____
Cardiac Failure	YES / NO	_____
		_____
Intermittent Claudication	YES / NO	_____
		_____
Thyroid Disease	YES / NO	_____
		_____
Family History of endocrine or other illnesses	YES / NO	_____
		_____
		_____
Previous Sympathectomy	YES / NO	_____
		_____
Other illnesses / operations	YES / NO	_____

ALCOHOLIC INTAKE (in an average week) _____

_____

_____

DIABETIC CONTROL

Good (< 9 mmol/l)

Fair (9.1 - 13.9 mmol/l)

Bad (14.0 mmol/l or more)

RETINOPATHY None / Background / Exudative / Proliferative

NEPHROPATHY None / Intermittent / ++ / +++

PERIPHERAL NEUROPATHY

		If "YES"
Numbness	YES / NO	Mild / Moderate / Severe
Paraesthesiae	YES / NO	Mild / Moderate / Severe
Burning Pains	YES / NO	Mild / Moderate / Severe
Muscle Weakness	YES / NO	Mild / Moderate / Severe

Findings on examination: _____

_____

_____

Symptomatic Peripheral Neuropathy PRESENT / ABSENT

AUTONOMIC NEUROPATHY

		If "YES"
Postural hypotension	YES / NO	Mild / Moderate /Severe
Dysphagia	YES / NO	Mild / Moderate / Severe
Epigastric Fullness	YES / NO	Mild / Moderate / Severe
Constipation	YES / NO	Mild / Moderate / Severe
Intermittent diarrhoea	YES / NO	Mild / Moderate / Severe
Hypoglycaemic unawareness	YES / NO	Mild / Moderate / Severe
Diminished sweating in legs	YES / NO	Mild / Moderate / Severe
Gustatory sweating	YES / NO	Mild / Moderate / Severe
Bladder dysfunction	YES / NO	Mild / Moderate / Severe
Cardiovascular A.N. tests	NORMAL / ABNORMAL	

Symptomatic Autonomic Neuropathy PRESENT /ABSENT

IMPOTENCE PRESENT / ABSENT

If "PRESENT", Durations _____ months.

If "PRESENT", Details _____

_____

_____

If "ABSENT", Temporary impotence in the past YES / NO

Details if "YES" _____

_____

LIBIDO NORMAL / INCREASED / DECREASED

EJACULATION PRESENT / ABSENT

NORMAL / ABNORMAL

Details if "ABNORMAL" _____

_____

_____

_____

APPENDIX B

Collaborative studies with the MRC Reproductive Biology Unit

The following article has been submitted for publication. The studies were carried out by Drs. John Bancroft and Christopher Bell. Apart from supplying patients with known potency/impotency, clinical characteristics and cardiovascular autonomic tests and apart from acting as a normal control subject, my only contribution to this work was in the "blind evaluation" of the tracings used to place each erection in a certain "type."

These data are included because this study formed part of the overall concept of this thesis and because the collective knowledge obtained from these data influenced the thinking of all the collaborators. The "message" from this study has implications for the evaluation and approach to management of many men with "diabetic impotence."

PSYCHOPHYSIOLOGICAL ASSESSMENT OF PENILE ERECTION

A NEW APPROACH

I METHODOLOGY AND RESULTS IN NORMAL SUBJECTS

by

John Bancroft and Christopher Bell

INTRODUCTION

In recent years there has been increasing recognition that many cases of erectile dysfunction are due, at least in part, to physical factors. This has led to a renewed interest in the physiological mechanisms of normal erection and the search for methods of investigating erectile function that may have diagnostic value.

The traditional view that erection is produced by arteriolar vasodilation under the control of the parasympathetic outflow and mediated cholinergically has been recently challenged (Bancroft, 1970; Wagner, 1982). There is now evidence that in addition to increased arterial flow, the reduction of venous drainage is involved (Brindley, 1983) and the closure of arterio-venous shunts may also be important (Wagner et al, 1982).

Most methods of investigating erectile dysfunction now in use are concerned with the physiological state of the non-erect penis (e.g. measurement of penile blood pressure, Abelson 1975; Velcek et al, 1980) or involve invasive procedures (e.g. arteriography and 'artificial erection', Michal, 1982), "xenon washout", (Wagner & Uhrenholdt, 1982) or measure erections during sleep, the relevance of which to erotic response and normal sexual activity is not yet clear (Schiavi & Fisher, 1982).

In the first part of this paper we describe a method of investigating erectile responses to erotic stimuli in the laboratory, which allows not only measurement of penile diameter change but also penile blood flow. Comparison of these two variables may throw light on the relative importance of the different components of erection and the factors that influence them. The use of the method in comparing men with and without erectile failure of different kinds is reported in the second part.

Methods

In addition to penile diameter, the following cardiovascular parameters were monitored: penile and ear blood flow (recorded photometrically), systolic and diastolic blood pressure. All parameters were recorded on a Grass model 7D polygraph. Details of the techniques used are as follows:-

Penile Diameter

A standard mercury-in-rubber strain gauge with platinum electrodes was used and connected to the 7PIE D.C. preamplifier via a Wheatstone Bridge (Karacan, 1969). The strain gauge was calibrated prior to each test using two perspex discs of diameters 25 and 26 mm. (the relationship between diameter and deflection is linear beyond the range used).

Arterial pulse photometry

For measurement of penile pulse, we used a reflectance photometer incorporating an R.S. 586-447 light emitting diode and a Clarex 904L photoelectric cell (Fig. 1). The device was coupled to a Grass wide band AC EEG preamplifier 7P5B, via the circuit shown in Fig. 2. A Grass transmittance photometer (PTTI) was applied to one ear lobe to provide a measure of peripheral arterial flow, and a record of heart rate so that the penile pulse could be confirmed as being due to arterial pulsation. The PTTI was coupled to a Grass 7P4 preamplifier. In some subjects a PTTI was used in addition to record digital pulse.

The principle underlying photelectric pulse detection is that light of appropriate wavelength, directed through the skin, is absorbed by the underlying tissue in proportion to the amount of blood in the local vasculature: pulsatile fluctuations off blood movement associated with cardiac ejection can be recorded using a photoelectric detector to measure either the light reflected from the tissue or that transmitted through it (Hertzmann, 1937; Rawson, 1959). Although it is not possible to calibrate

the signals obtained in terms of absolute flow units, there is substantial in vitro evidence that the amplitude of the pulse recorded is proportional to pulsatile flow though volume pulsation of blood vessels may also contribute to the signal (Jennings et al. 1980).

In the case of the penis, circulatory changes during sexual arousal could conceivably lead to artefactual changes in penile arterial pulse through several mechanisms.

1. Penile engorgement might alter the amount of light reflectance by changing the distance between transducer and blood vessels or by compressing the vessels against the transducer. We examined these possibilities by using the penile reflectance photometer applied to the fingers of two subjects while interposing perspex spacers (1mm-20mm) between transducer and skin, and while inflating a pediatric blood pressure cuff around finger and transducer to different pressures. We found that, provided incidental light was excluded, variations in distance between detector and skin had negligible effects unless more than about 10mm and that increasing pressure had no effect unless sufficient for arterial compression (i.e. 80 mm Hg or more).

2. Alterations in resistance to flow caused by erectile engorgement might modify the signal. We therefore examined digital pulses during inflation of a forearm cuff to 60 mm Hg in order to increase venous pressure (2 subjects) and during application of a tight rubber band around the finger distal to the pulse detector (5 subjects). Neither manoeuvre altered pulse amplitude. By contrast, local increase in arterial flow induced by immersion of the finger in water at 44°C caused substantial increase in pulse amplitude (4 subjects), while generalised increase in peripheral resistance induced by a 30 second period of immersion of one foot in water at 5°C caused reduction of pulse amplitude in 8 of 9 subjects. We therefore felt justified in

concluding that the penile pulse signals recorded are an appropriate index of penile arterial flow and are not likely to be seriously distorted by other events occurring during erection.

The penile photometer used in this study and its position of attachment are shown in Figure 1. After much experimentation we devised a method of attachment using a piece of adhesive chiropodist's felt of a size which, when fixed to the stretched skin of the penis, will pass no more than halfway round the circumference and keep the photocell in good contact with the skin (Figure I).

In order to obtain a signal from the dorsal arteries the photocell was positioned at the dorsal midline. It is necessary to avoid placing the photocell directly over a vein. Care in attachment is important and often an unsatisfactory signal can be improved with re-attachment and slight re-positioning*. The photocell is sensitive to body movement, hence the positioning of the lead is also important; clothing should be kept well clear.

Blood Pressure

A standard sphygmomanometer cuff containing a microphone (Sharpe MB 200) was coupled to a Grass 7P8C sphygmomanometer preamplifier and inflated automatically every 30 seconds with controlled deflation. This allowed measurement of systolic and diastolic (Phase IV) pressures.

Since completing this study, we have been able to use a Doppler probe to identify the position of the dorsal artery. This improves the quality of the signal obtained. It has also shown that other sites more laterally can be used by careful Doppler searching and these presumably reflect signals from the deep penile arteries.

Procedure

As sexual responses in the laboratory setting are obviously susceptible to psychological factors, much care was taken to optimise conditions and to keep them as constant as possible. The procedure used was as follows. The subject was in a small room, kept at a temperature of approximately 70°F, containing an easy chair and a television set, and joined by a door to a laboratory containing the Grass polygraph, automatic cuff inflating machine and video cassette recorder. The subject was asked to remove or lower his trousers well clear of his penis. A towel was provided to place over his lap. He was then asked to fit both devices whilst left alone in the room. Afterwards, their position was checked by visual inspection and once a satisfactory signal was obtained from them the ear photometer and blood pressure cuff were fitted by the experimenter. The subject was then asked to remain seated, comfortably but avoiding unnecessary movement and to watch the television screen (i.e. a normal non-erotic programme) for a baseline period of approximately 10 minutes during which all parameters were recorded.

The testing procedure lasted approximately one hour, and was carried out in identical fashion on two separate occasions. The average interval between occasions was 33 days (range 13-53 days).

Erotic Stimuli

Two types of erotic stimuli were used, fantasy and film. For fantasy, the subject was asked to produce as exciting an image as possible and to maintain it until asked to stop. He was told that he would not be asked details of the fantasy. The film extracts were each 2 to 3 minutes long, showing explicit sexual activity (sexual intercourse and oral-genital contact). One extract involved two women and one man, the remainder involved one couple only. Five film extracts were used, one on both testing

occasions, the others being used only once.

The order of presentation of stimuli in each session was as follows: First fantasy (3 minutes), 3 film sequences, and second fantasy (3 minutes). A minimum of 3 minutes was left between each stimulus, or longer if necessary to allow the penile diameter to return to baseline.

Subjects

Normal volunteers were recruited from hospital and Research Unit staff. The initial approach was tentative so that it was easy for the individual to decline without embarrassment. If there was apparent willingness, a more definite request was made. Each subject was told that we required men with no obvious erectile problems as a comparison group for impotent men.

Twenty-two volunteers were tested, mean age 38.2 years (S.D. 10.3, range 24-53). Three subjects were unable or unwilling to return for the second testing session (mean age 34).

Interpretation of physiological data

A typical "normal response" is shown in Figure 3. The following parameters were measured in each response, and are shown in Figure 3.

1. Maximum penile diameter change.
2. Latency of erectile response to 2.5mm, 5mm and 10mm increase in diameter.
3. Baseline penile pulse amplitude. The AC signal was samples for a 10 second period, at least 30 seconds prior to the onset of each erotic stimulus. The "cleanest" sample closest to that time point was taken. The mean amplitude in uVolts was calculated.
4. Penile pulse amplitude increase during erotic stimulation (a) the "increase" from preceding baseline to maximum and (b) the "difference" between maximum and minimum during erotic stimulation.

5. The mean systolic and diastolic blood pressure was taken from the three measurements preceding each erotic stimulus. The highest systolic and diastolic levels during the stimulus presentation were then measured and the difference between these and the baseline means taken as the blood pressure response to erotic stimulation.

Temporal relationship between penile probe amplitude and penile diameter change

It was evident that whilst both penile P.A. and diameter tend to change in response to erotic stimuli, they often do so at different times. Most typically, the penile P.A. starts to increase later than the onset of diameter change. Often there is considerable delay and in some instances the P.A. increase becomes much more noticeable after the erotic stimulus has ended and when the erection has started to decline. It is also common for there to be a decline in P.A., usually transient, in the early stages pf the erection, followed by a more substantial increase (See Figure 4). (This accounts for the pulse amplitude "difference" being greater than the pulse amplitude "increase").

The temporal relationship between changes in pulse amplitude and penile diameter was looked at in the first 12 subjects tested, by taking the largest erectile response in each case. Five second samples of penile diameter, penile pulse amplitude and pulse amplitude in the ear were taken every 20 seconds starting during the baseline period and continuing through until the erection was declining. Penile pulse amplitude was then correlated with penile diameter and ear pulse amplitude, based on change scores (i.e the differences between consecutive five second sample intervals.

To investigate these various temporal relationships further we described 6 patterns or types of response (Types I to IV are shown diagramatically in Figure 6 and examples of each are shown in Figures 7 to 10). Types V and VI involved increase in diameter with no increase in P.A. and vice versa. The operational definitions of each type are given in the appendix.

Responses were categorised by two independent observers. There was initial agreement for 75% of responses. Disagreements were then negotiated and resolved by applying the operational criteria more rigorously. It should be emphasised that this method of categorisation is a crude attempt to distinguish between temporal relationships which vary in a continuous rather than discrete fashion.

Interpretation of response latencies has proved to be complex as latency to 2.5mm and 5mm are not independent of the final degree of erection obtained. An analysis of this data, which is of theoretical interest, will be published separately.

RESULTS

Penile Diameter

For none of the variables was there a significant difference between the first and second sessions. The results will therefore be presented as means for all 22 subjects (i.e including those tested only once) (See Table 1). The percentage of subjects showing at least one response and the percentage of all possible responses reaching the criteria of 2.5, 5 and 10mm increase in diameter are also shown in Table 1.

Penile diameter changes in response to films were significantly greater than those to fantasy ($t=5.4$, d.f.20, $p = 0.001$), though two subjects responded more strongly to fantasy than to film. It should be emphasised, however, that this experiment was not designed to compare the relative

efficacy of these two types of stimuli.

Age was negatively correlated with mean penile diameter increase to fantasy ($r = -0.45$, d.f.20, $p = 0.05$) but not to film ($r = -0.06$).

Penile Pulse

Measureable pulse amplitude (P.A.) was recorded in all but two sessions. The main difficulty in interpreting the signal during erotic stimulation resulted from rhythmic increases in penile diameter, assumed to result from contractions of the perineal muscles, which produce marked interference with the photometric signal. In one session these artefacts were so frequent that the photometric signal was uninterpretable. In 17 other sessions, these contractions occurred, but the P.A. could be measured between them. Subjects showing these contractions were significantly older than those who did not (mean age 44.6 $\pm$ 8.1, n=9; 33.5 $\pm$ 9.1, n=13: $t = 2.95$, $p = .01$), but these two groups did not differ significantly in the degree of erection obtained.

Mean P.A. measurements during baseline periods and erotic stimulation are shown in Table 1. For all statistical procedures, log transformations of the microvolt values were used.

There was no significant correlation between pulse amplitude (either baseline or change) and age. Mean change in pulse amplitude (P.A.), however, did correlate with the degree of erection (for PA "increase" $r=0.44$, d.f.17, $p = 0.05$, one-tailed; PA "difference" $r=0.7$, d.f.17, $p = 0.001$).

Temporal relationship between penile pulse amplitude and diameter

In the first 12 subjects the correlations between penile pulse amplitude and diameter were extremely variable. Only three were significant, two were negative and one positive. The distribution of responses into the 6 categories is shown in Table 2 for the 18 men with

two categorisable sessions each. The distribution was significantly different in session 2, which showed more Type I and fewer Type II, III, IV and V responses (X_2 = 12.64, d.f.=6, p= 0.05). Percentages of each type of erection which were in response to fantasy were as follows: type I, 28%; II, 16%; III, 30%; IV, 38%; V 47% and VI, 89% (X_2 = 23.6, d.f.5, p= 0.001). Thus Type VI responses were particularly likely to occur with fantasy stimulation. More data will be required before the functional significance of these different types can be properly assessed. Types I and II erections, however, tended to be larger and more rapid than Types IV and V.

Blood Pressure

The baseline levels and changes in blood pressure during erotic stimulation are shown in Table 1.

Mean blood pressure responses to erotic films were significantly greater than those to fantasy (systolic, t=4.11, d.f.17, p= 0.001; diastolic, t=2.65, d.f.17, p= 0.05). The basis of the blood pressure rise was examined further in some subjects by comparing finger P.A. during erotic stimulation and during the cold pressor test (30 second period of emersion of one foot into water at 5°C). Both stimuli produced comparable increases in blood pressure (Chris Bell to complete

).

However while the cold pressor test was associated with a reduction in digital P.A. by 20-90% in 8 out of 9 subjects tested, during erotic stimulation the increased blood pressure was accompanied by a reduction of digital P.A. in only 3 of 10 subjects tested, and in 4 there was a substantial increase in amplitude (by 40-60%). Lack of reduction in digital P.A. during erotic responses therefore indicates no increase in peripheral resistance and suggests that the blood pressure rise is due primarily to increased cardiac output.

DISCUSSION

This study has demonstrated an effective method of eliciting erections in normal subjects in response to visual stimulation. Eighteen out of 22 subjects (82%) responded with more than 10mm increase in penile diameter on at least one occasion; only one subject failed to respond with an increase of more than 5mm. Responses to fantasy were less strong and less frequent, but 7 subjects (32%) produced erections greater than 10mm diameter increase, and in two subjecs their responses to fantasy were greater than those to film.

Only in response to fantasy did we find a correlation between erection and age. This may be because the film stimulus was strong enough to obscure the age effect. Alternatively, mechanisms involved in fantasy response may be more susceptible to ageing. It is of possible relevance that in a study of hypogonadal men, androgen withdrawal and replacement had an effect on their erectile responses to fantasy but not to film, which remained within the normal range even during androgen withdrawal (Bancroft & Wu, 1983).

In addition to erection there was a predictable increase in systolic and diastolic blood pressure in response to erotic stimulation, more marked for film than with fantasy. It was of some interest that this pressor response was not associated with any evidence of decreased peripheral blood flow, in contrast to the response to the cold pressor test, and the room temperature was insufficient to cause thermoregulatory vasodilation of an extreme degree. We therefore conclude that the pressor response to erotic stimuli was due primarily to increased cardiac output rather than increased peripheral resistance.

We have shown that measurement of pulse amplitude photoelectrically from the dorsal surface of the penis is a practical and effective non-invasive procedure providing that sufficient care is taken with placement and method of fixing the photocell to the skin. Use of a Doppler probe to locate the artery should enhance the efficacy of this method.

Although we hope to obtain more direct physiological validation of this photometric signal, we believe it justified to assume that it monitors penile arterial flow, mainly through the dorsal penile arteries but, with appropriate placement, from the deep arteries also. Whereas an increase of pulse amplitude during the development of erection was usual, it was by no means invariable and was usually later in onset than the increase in penile diameter. A recent study of temperature change during erection in normal subjects reported comparable findings (Webster & Hammer, 1983). One out of eight normal subjects showed an increase in penile skin temperature, presumably reflecting arterial flow, which occurred after the erectile response was declining, suggesting a temporal pattern similar to our type IV response.

Despite the evidence detailed under Methods to indicate that the photometric records we obtained did represent pulsatile changes in penile arterial flow, certain other explanations for the variations in pulse amplitude seen must be considered:

(a) Pressure effects. Reduction in pulse amplitude during erection could be due to increasing pressure on the photocell. Apart from the unlikelihood of this, given the method of fixing the photocell used, this explanation could not account for the fact that pulse amplitude frequently decreased and then returned whilst erection continued to develop. Also reduction of pulse amplitude sometimes occurred after the onset of the erotic stimulus and before any erection had developed (e.g. Fig.9). Similarly, increase in pulse amplitude occurred after cessation of the erotic stimulus and in the

absence of any penile diameter change. Pressure effects are not a sufficient explanation for these phenomena.

(b) Positional effects. The temporal relationship of pulse amplitude and diameter change may vary according to the position of the photocell on the penis. However, variations of this relationship not only occurred between individuals and between sessions, but also within sessions when the photocell position was constant.

(c) Anatomical factors. The relative lateness of pulse amplitude change in the dorsal artery, compared with diameter increase of the shaft may be because the dorsal artery principally supplies the glans rather than the corpora cavernosa. Apart from the variability of this temporal relationship within the same subject, and the improbability of differential timing of blood flow in the dorsal and deep penile arteries, we also found that in 2 subjects that were investigated, tumescence of the glans had no closer temporal relationship with pulse amplitude change than shaft tumescence.

(d) Straightening of penile arteries. Michal (1982) reported that during the induction of artificial erection by means of saline infusion into the corpora cavernosa, there is a "selective dilation" of the penile arteries, as shown on arteriograms, which is at least in part due to the straightening of the otherwise tortuous vessels. Such straightening could result in increased flow in those vessels. During normal erection, lengthening of the penis in the early stages would also lead to straightening and hence increased arterial flow. This process could account for the relative delay in pulse amplitude increase that we have observed but not the decrease in pulse amplitude during erection or the increase that occurs once the erection starts to decline.

It is therefore likely that our recordings of pulse amplitude do represent changes in arterial inflow to the penis, and our results indicate that increased arterial flow is associated with erection in the majority of

normal individuals. It appears, however, that arterial changes are typically not essential for the early stages of erection, which presumably depend on venous mechanisms or the regulation of intrapenile shunts (Wagner et al, 1982). Nevertheless, it is possible that where arterial inflow increases early, erection is more efficient and such arterial changes may be necessary for the development of sufficient rigidity for vaginal entry.

This relative independence of arterial and other mechanisms implies different control mechanisms, which may be differentially affected by arteriopathic, neuropathic, pharmacological or psychological factors. It may be that change in arterial flow is part of a more generalised sexual arousal response, whereas the other erectile erectile mechanisms are part of a more stimulus-controlled genital response. This would account for the tendency for pulse amplitude increase to persist after the penile diameter has returned to baseline.

The delay or dissociation of the arterial component may be due to psychological inhibition. This is consistent with our finding that such delay was less likely to occur in the second session when presumably psychological inhibition was less marked.

The possibility that measurement of penile pulse amplitude and its temporal relationship with penile circumference change, may reflect abnormalities of penile blood vessels, their neurological control or psychological inhibition will be explored further in the second paper when responses in clinical subjects will be reported.

ACKNOWLEDGEMENTS

We are indebted to George Burt for designing and producing the photometer and blood pressure cuff inflating machine. We are also grateful to Dr. David McCulloch for his help in 'typing' the erectile responses, and to our 22 subjects for their tolerance and responsiveness.

APPENDIX

TYPOLOGY OF ERECTIONS

1. The determining characteristic is the temporal relationship between pulse amplitude (P.A.) change and volume change. A normal (type I) erection shows a parallel increase in these two variables. A delayed (type II) pattern shows P.A. increase starting later than volume increase. A transient P.A. response shows P.A. increasing during the early stages of volume increase but not continuing into the later stages (type III). A dissociated response (type IV) shows P.A. tending to increase when volume is going down and vice versa. P.A. increase without volume change is called type VI and volume change without P.A. increase is called type V.

2. (a) For pulse amplitude (P.A.) increase to occur, it should have doubled its previous lowest levels for at least 10 seconds.

(b) For volume increase to occur, the penile diameter should increase by 1 mm or more.

3. For type I, P.A. increase should be maintained (i.e. above criterion level) up to the point of maximum volume and should have reached criterion level before the 50% diameter increase is reached. (A transient decrease below criterion level may occur during diameter increase. Providing that it does not remain below the criterion level for longer than 20 seconds, it can be ignored).

For type II, P.A. increase should be maintained up to maximum volume, but it reaches criterion after the 50% volume increase is reached.

For type III, P.A. increase is not maintained up to maximum volume (i.e has decreased below criterion before maximum volume is reached or when the maximum P.A. is prior to 50% volume increase and then shows a substantial decline).

For type V, P.A. increase does not reach the criterion, but volume increase does.

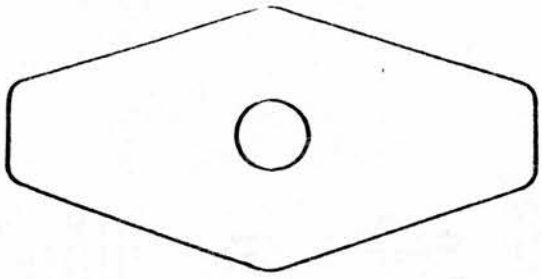
For type VI P.A. increase reaches criterion no later than 10 seconds after end of erotic stimulus but volume increase does not.

Type IV erections have 3 sub-types:-

IV (a) - P.A. increase reaches criterion but only after the diameter has started to decline (i.e. by at least 25% of the maximum). Or if it continues to increase (i.e. reaches maximum) beyond the point of 25% diameter reduction.

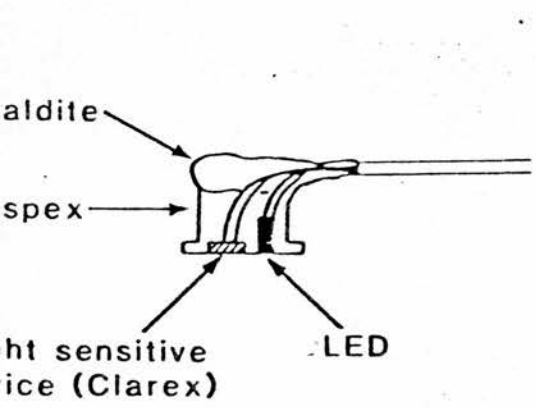
IV (b) - P.A. increase reaches maximum in 10 seconds or longer after the end of the erotic stimulus but within 90 seconds regardless of what happened before.

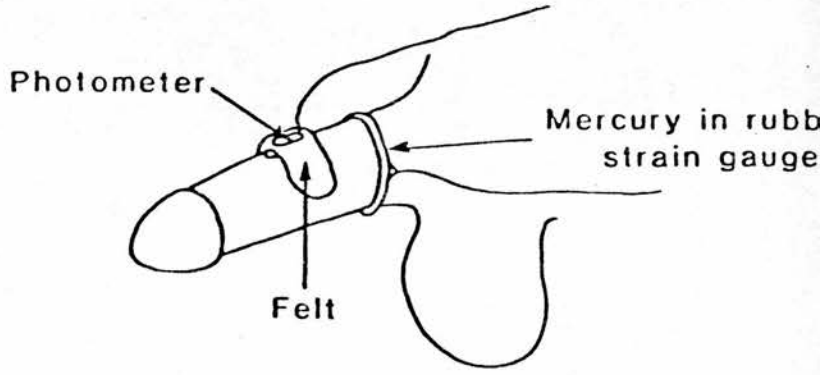
V (c) - P.A. shows predominantly a decrease (below 75% baseline level) for duration of the stimulus or the duration of the diameter increase. Include under V (c) those responses where there is a P.A. increase only before the volume starts to increase, when the P.A. then shows a decline.



Chiropodist's adhesive
felt 2·5mm thick

FELT ATTACHMENT





PHOTOMETER

FIGURE 1

Penile photometer and method of fixing. The piece of adhesive felt measures 55 mm x 30 mm. The diameter of the photocell is 10 mm.

CIRCUIT FOR PENILE PHOTOMETER

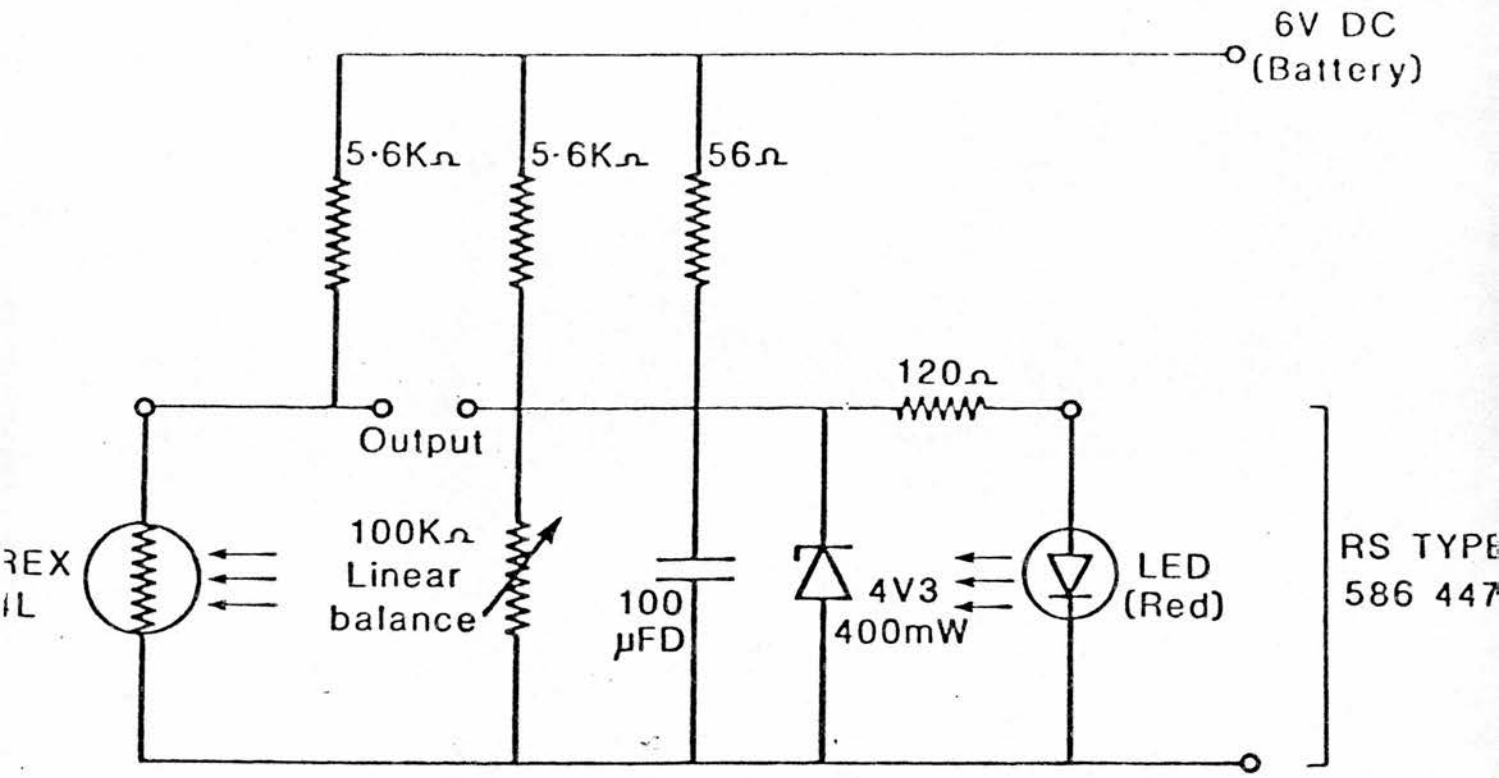
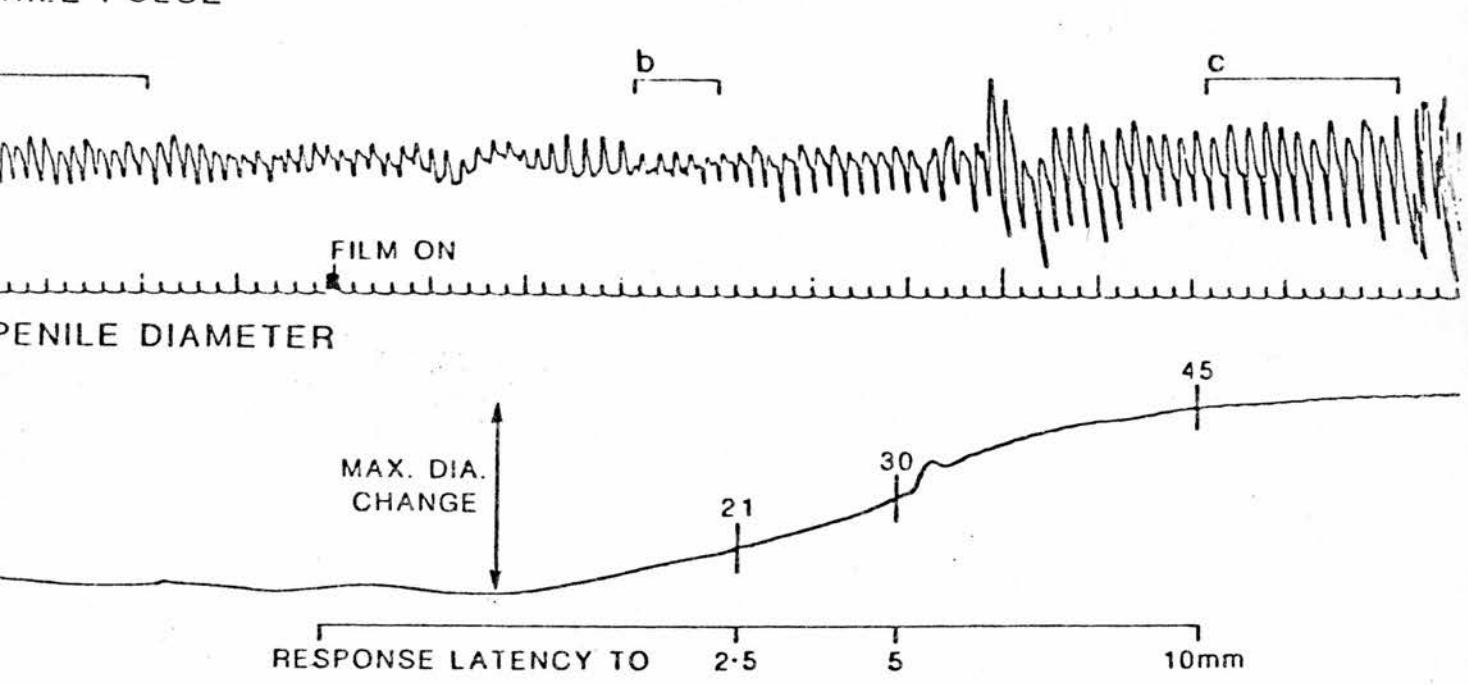


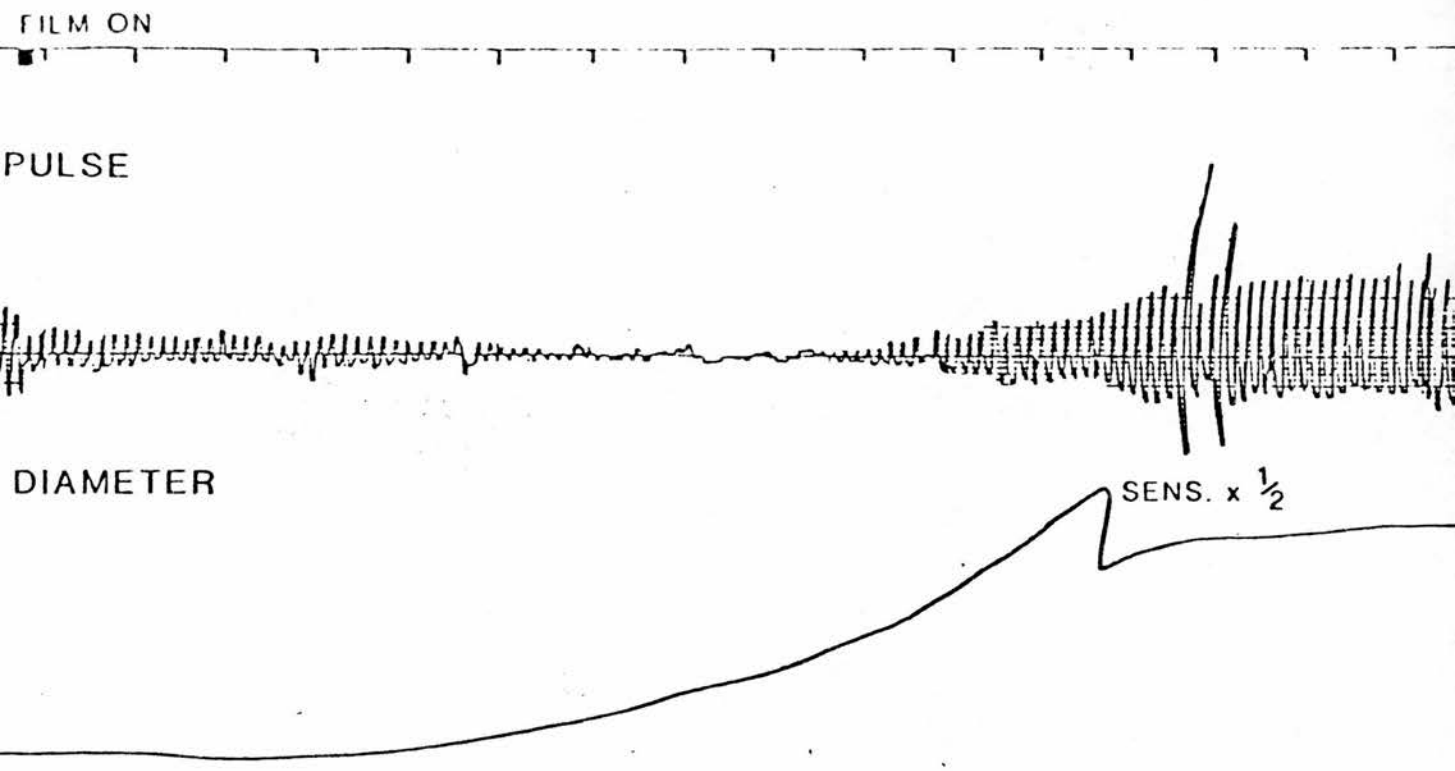
FIGURE 2

Circuit Diagram for the penile photometer.



IGURE 3

typical normal response showing the variables measured in each case.
. Maximum penile diameter change. 2. Latency of erectile response to
.5 mm, 5 mm and 10 mm (in this case 21, 30 and 45 seconds respectively).
. (a) Baseline pulse amplitude during a 10 second period. (This would
ormally be sampled at least 30 seconds prior to the onset of the
timulus. (b) the minimum mean pulse amplitude during a 5 second period
nd (c) the maximum mean pulse amplitude during a 10 second period.
ulse amplitude 'increase' is c-a, 'difference' is c-b.



IGURE 4

ypical example of transient decline of pulse amplitude during the evelopment of an erection. This pattern occurred to some extent in 5% of erectile responses.

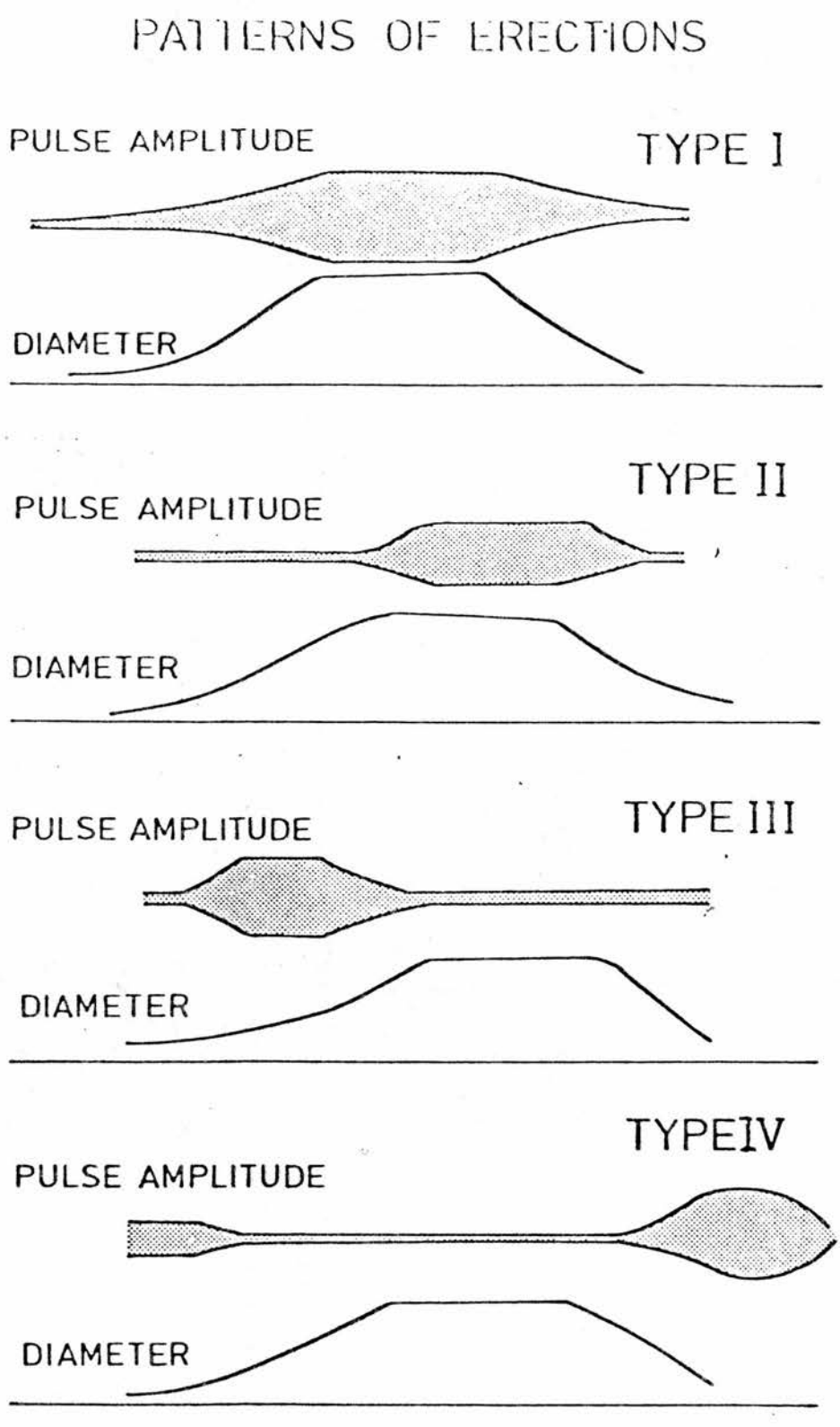


FIGURE 5

Diagramatic representation of the different 'types' of erectile response showing different temporal relationships between penile diameter and pulse amplitude changes.

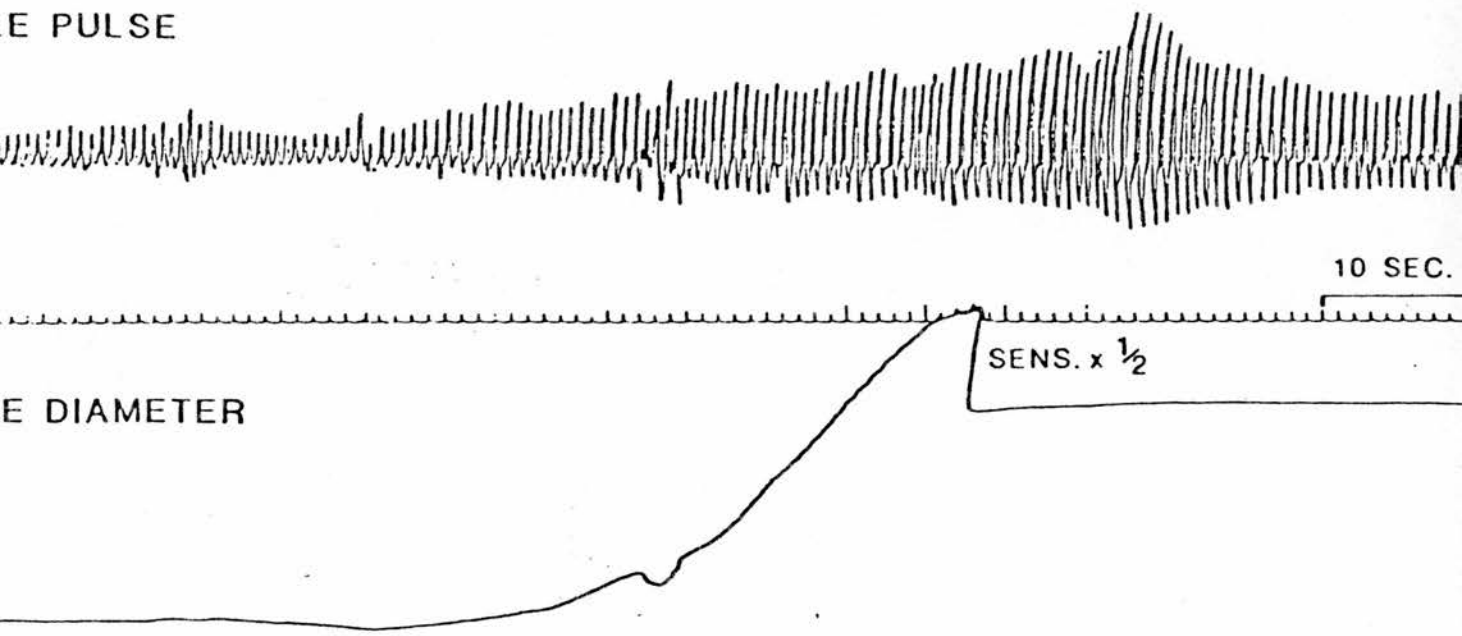


FIGURE 6

Type I erection showing pulse amplitude increase starting at the same time as the diameter change.

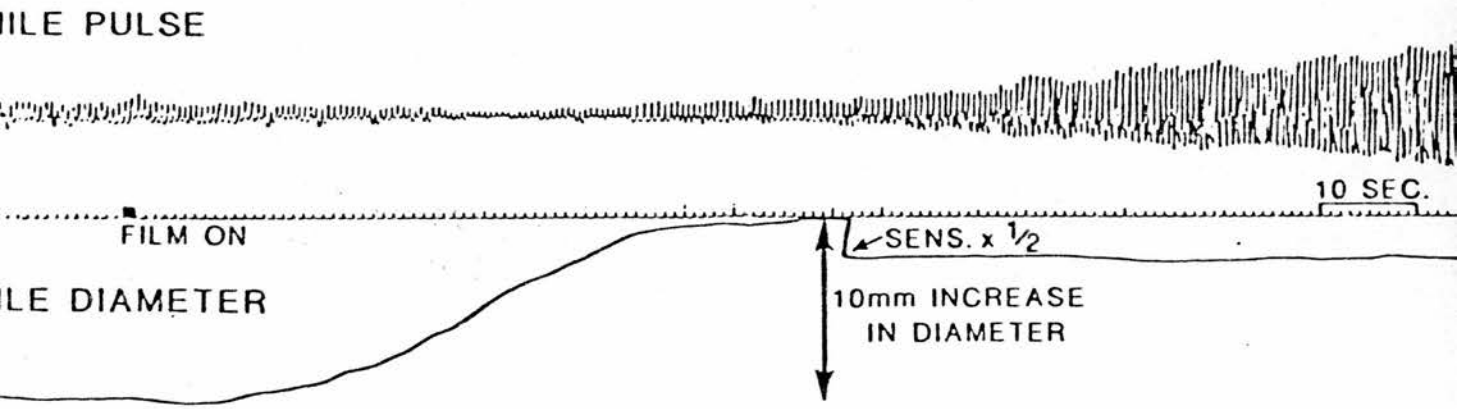
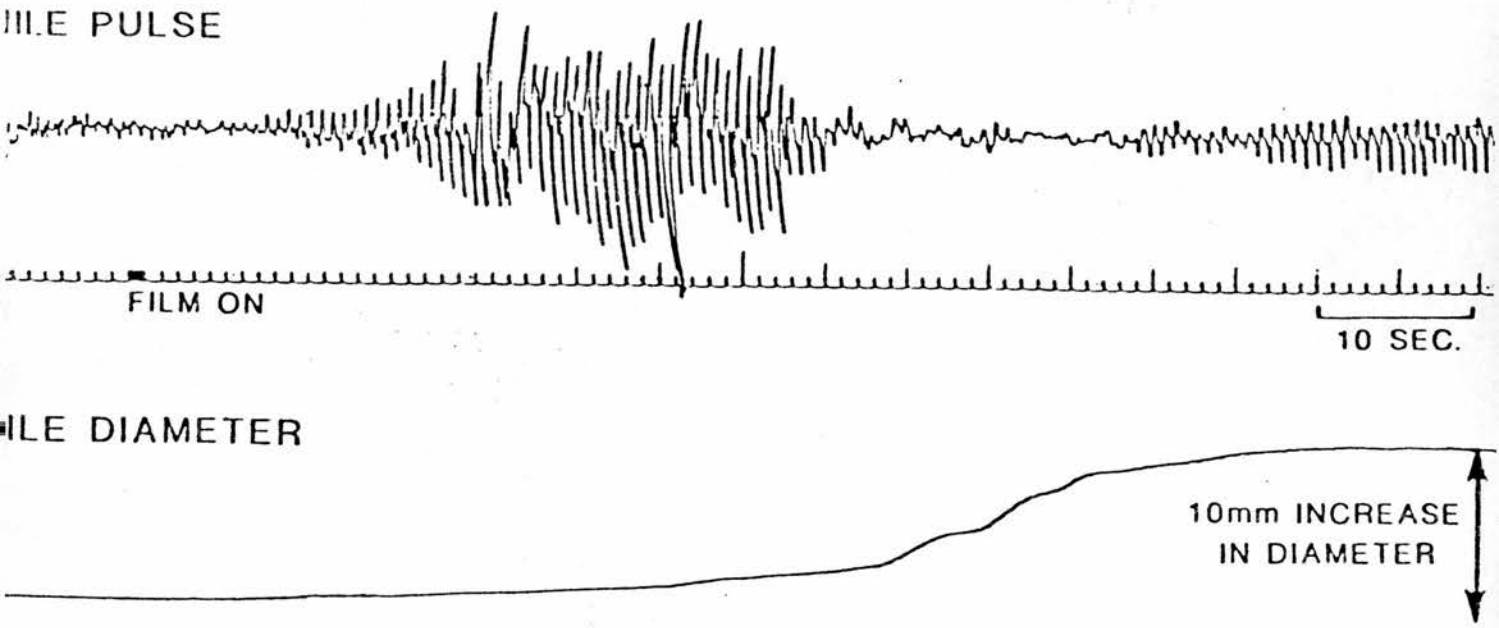


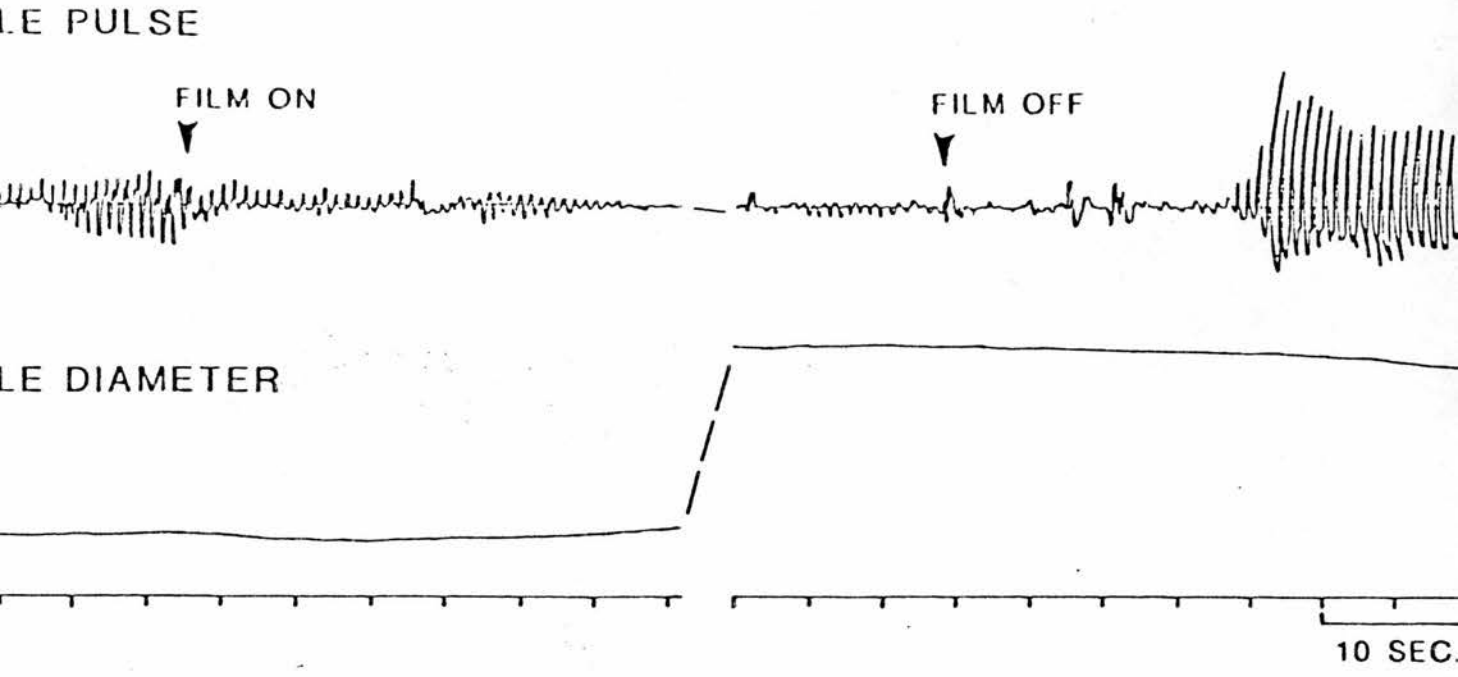
FIGURE 7

Type II erection. The pulse amplitude increase occurs late when the diameter change is already close to maximum. This is from the same subject as in Figure 7, but came from the first session, whereas the type I response was from the 2nd session. Note how the type II erection is slower to develop.



GURE 8

'pe III erection showing a large but transient pulse amplitude change
ly during the early stages of diameter change .



GURE 9

pe IV erection. This tracing shows the first and last part of the sponse. In this intervening period there was a slow, gradual increase in nile diameter whilst the pulse amplitude remained very small. Note how e pulse amplitude reduces as soon as the erotic stimulus is switched on d finally returns with increased amplitude after the end of the stimulus en the erection is just beginning to decline.

TABLE 1

CHANGES IN PENILE DIAMETER, PENILE PULSE AMPLITUDE IN 22 NORMAL MEN IN RESPONSE TO EROTIC FANTASY AND FILM.

		Mean Baseline	Response to Fantasy	Response to film
Penile diameter	Mean	26.7mm	+4.6mm	+9.1mm
	S.D.	2.7	4.3	3.0
Increase in penile diameter greater than:-				
2.5mm	% subjects		73%	100%
	% responses		44%	95%
5mm	% subjects		55%	95%
	% responses		35%	81%
10 mm	% subjects		32%	82%
	% responses		21%	42%
Penile pulse amplitude (P.A.) µV	Mean	659	-	-
	S.D.	±508		
Increase	Mean	-	+750	+1209
	S.D.		±1150	±1159
Difference	Mean	-	1194	1643
	S.D.		±1270	±1385
Blood Pressure	mm Hg			
Systolic	Mean	119.1	+16.4	+24.6
	S.D.	±13.8	±7.8	±11.1
Diastolic	Mean	75.4	+14.9	+16.6
	S.D.	±11.8	±9.5	±8.9

TABLE 2

INCIDENCE OF DIFFERENT TYPES OF ERECTION. PERCENTAGE OF RESPONSES TO FANTASY AND FILM IN 18 MEN

	I	II	III	IV	V	VI	No Response	Not Classifiable	
SESSION 1.	16	29	9	19	11	5	8	2	Comparison of Sessions 1& 2
SESSION 2.	38	20	2	15	7	6	9	2	X_2 = 12.64 6 d.f. p = <0.05
TOTAL	27	25	6	17	9	5	9	2	(excluding "not classifiable")

REFERENCES

ABELSON, D. (1975). Diagnostic value of the penile pulse and blood pressure. A Doppler study of impotence in diabetics. J. Urol. 113, 626.

BANCROFT, J. (1970). Disorders of sexual potency. In Modern Trends in Psychosomatic Medicine. Ed. O.W. Hill. Butterworths, London.

BANCROFT, J. & WU, F.C.W. (1983). Changes in erectile responsiveness during androgen replacement therapy. Archives Sexual Behavior 12, 59-66.

BRINDLEY, G.S. (1983). Sexual function and fertility in paraplegic men. In Male Infertility. Ed. T. Hargreave. Springer Verlag, Berlin.

HERTZMANN (1937). Photo-electric plethysmography of the fingers and toes in man. Proc. Soc. Exp. Biol. Med. 37, 529-34.

JENNINGS, J.R., TALNMONSH, A.J. & REDMOND, D.P. (1980). Non-invasive measurement of peripheral vascular activity. In Techniques in Psychophysiology. Ed. Martin, I. & Venables, P.H. Wiley, Chichester, p.86-116.

KARACAN, I. (1969). A simple and inexpensive transducer for quantitative measurement of penile erection during sleep. Behav. Res. Meth. & Instrum. 1, 251-252.

MICHAL, V. (1982). Arterial disease as a cause of impotence. Clinics in Endocrinology and Metabolism 11 (3) 725-748.

RAWSON, R.O. (1959). A highly sensitive miniaturised photoelectric plethysmograph. J. Appl. Physiol. 14, 1049-1050.

SCHIAVI, R.C. & FISHER, C. (1982). Assessment of diabetic impotence: measurement of nocturnal erections. Clinics in Endocrinology and Metabolism 11, No.3, 769-784.

VELCEK, D., SNIDDERMAN, K.W., VAUGHAN, E.D., SOS, T.A. & MUECKE, E.C. (1980). Penile flow index utilising a Doppler pulse wave analysis to identify penile vascular insufficiency. J. Urology 123, 669-673.

WAGNER, G. (1982). Vascular mechanisms involved in erection and erectile disorders. Clinics in Endocrinology and Metabolism 11, No.3, 717-723.

WAGNER, G., BRO-RASMUSSEN, F., WILLIS, E.A. & NIELSON, M.H. (1982). New theory on the mechanism of erection involving hitherto undescribed vessels. Lancet ii, 416-418.

WAGNER, G. & GREEN, R. (1981). Impotence. Physiological, Psychological, Surgical Diagnosis and Treatment. New York, Plenum Press.

WAGNER, G. & UHRENHOLDT, A. (1980). Blood flow measurement by the clearance method in the human corpus cavernosum in the flacid and erect states. In Vasculogenic Impotence. Proceedings of the First International Conference on Corpus Cavernosum Revascularisation, 1980. Ed. Zorgniotti, A.W. & Rossi, G. pp. 41-46. Springfield II. Thomas.

WEBSTER, J.S. & HAMMER, D. (1983). Thermistor measurement of male sexual arousal. Psychophysiology 20

PSYCHOPHYSIOLOGICAL ASSESSMENT OF PENILE ERECTION

A NEW APPROACH

2. ASSESSMENT OF ERECTILE FUNCTION IN DIABETIC AND NON-DIABETIC IMPOTENCE

John Bancroft, Christopher Bell, Basil Clarke,

David Ewing, David McCulloch and Pamela Warner

INTRODUCTION

Although measurement of erectile response to erotic stimuli in the laboratory has been used for many years to assess sexual preferences and outcome of modification of deviant sexual behaviour (Bancroft, 1974), little attention has been paid to its use in the diagnosis of erectile dysfunction. One exception is a study by Kockott et al (1980).

In this paper, we report the use of non-invasive psychophysiological testing of erectile and other responses to erotic stimuli, in the comparison of three groups of men, normal subjects, and non-diabetic and diabetic men with erectile dysfunction. The results from a small group of diabetic men without erectile problems will also be reported.

Methods

The method of testing and the physiological variables measured are described in full in Part 1. In this paper we will be reporting erectile responses (i.e. increase in penile diameter), penile blood flow (pulse amplitude change) and systolic and diastolic blood pressure change to both erotic films and fantasies. As described in Part 1, a variable temporal relationship between degree of erection and pulse amplitude change has been observed, leading to a typology of erections. Types I and II are considered to be "normal" responses which tend to be larger and more rapid than types IV and V. In type VI responses, only pulse amplitude change occurs.

Subjects

Twenty-two normal subjects (Group N) were described in Part 1. Their ages ranged from 24 to 53 (mean 38 years).

Twenty-five non-diabetic men with erectile problems (Group NI) were studied. Their ages ranged from 25 to 58 (mean 40). Included in this group was one case of traumatic paraplegia, impotence following colonic resection (one case), transverse myelitis (one case), Peyronies disease (one case),

ischaemic heart disease (one case) and hypertension (three cases).

Twenty-six diabetic men with erectile problems (Group DI) were studied, and had ages ranging from 25 to 53 (mean 42). The mean duration of their diabetes was 15 years (range 5-31 years). Twenty-two were insulin dependent and four were taking oral hypoglycaemic agents. The incidence of autonomic neuropathy was established by means of cardio-vascular reflex tests (Ewing & Clarke, 1982). The subjects were thus categorised into those with normal cardio-vascular reflexes (Group 1, n=6), those with parasympathetic damage only (Group PS, n=13) and those with parasympathetic and sympathetic damage (Group PS plus S, n=7). Following systematic recording of the state of the retina, subjects were categorised as (1) no retinopathy (n=8), (2) background retinopathy (n=9) and (3) exudative or proliferative retinopathy (n=8). Four diabetic men with no erectile problems were also studied (DN group). Their age ranged from 24 to 53 (mean 39).

Each subject in the two groups with sexual dysfunction (Groups NI and DI) was categorised, on the basis of history and physical examination, to indicate the likelihood of psychogenic causation. Three categories were used: (1) psychogenic causes not apparent, (2) present and possibly contributory and (3) present and probably the main causative factor. Performance anxiety was not considered as sufficient explanation for erectile problems as it is usually secondary to either psychogenic or organic factors.

The non-diabetic dysfunctional group were also categorised in a similar way to indicate the likelihood of organic aetiology. Transient physical episodes (e.g. painful circumcision, genital herpes) were regarded as contributory (organic category 2) but not sufficient causes.

Method of Analysis

Two types of analysis will be reported.

(a) Between Group Comparison

Three equal sized age-matched groups were taken from the original groups, first excluding those with only one session of testing or those in the NI group who had unequivocal (i.e. category 3) organic aetiology. This resulted in three groups of 19 each, ages (mean ± S.D.), N=31.9 ± 10.1, NI=39.2 ± 11.3 and DI=40.1 ± 7.9. The results will be presented as means of the two testing sessions combined.

(b) Within Group Comparison

Each of the original dysfunctional groups are also divided according to (1) the presence of psychogenic or organic factors and (2) in the case of the diabetic group, the presence or absence of (a) autonomic neuropathy and (b) retinopathy. Where more than one group was being compared, analysis of variance was used, together with Scheffé test for comparison between pairs of groups. Where only two groups were being compared, Students t-test was used. Logarithmic transformation of penile pulse amplitude scores was used in all cases.

RESULTS

Results for the degree of erection, penile pulse amplitude and systemic blood pressure changes for the three matched groups are shown in Table 1. The DI group produced significantly less erections in response to film than both the N and NI groups and significantly less response to fantasy than the N group. The N and NI groups were not significantly different in either case. A comparable pattern was found for the pulse amplitude difference . There were no significant differences in baseline systemic blood pressure or blood pressure change during erotic stimulation.

The distributions of the six types of erections in the three groups are shown in Figure 1 as percentages of all responses (i.e. types I-VI). Types I and II had very similar distributions within each subject group and are therefore shown combined. A significant Chi square was found for responses to both film and fantasy. This was mainly due, in the case of responses to film, to a disproportionately high number of types I and II in the N group, of type IV in the NI group and of type VI in the DI group.

For fantasy responses, there was a disproportionately high number of type I in the normal group and of type VI in the diabetic group. Thus types IV and VI may be of particular relevance in distinguishing between diabetic and non-diabetic (?psychogenic) impotence.

Non-Diabetic Men with Erectile Dysfunction

The 25 patients in this group were divided into two sub-groups according to the categorisation of psychogenic and organic factors: (1) those in whom psychogenic factors were considered to be of greater importance than organic factors ("psychogenic" group, n=17) and (2) those in whom organic factors were considered to be of either equal or greater importance than psychogenic factors (n=8). The principal results are shown in Table 2. The psychogenic group had significantly greater erectile responses to film but there was no difference in the response to fantasy.

The "psychogenic" and "organic" sub-groups did not differ in their pulse amplitude difference during erotic stimulation. There was also no marked difference in the distribution of the types of erection between the two groups although type VI erections (pulse amplitude increase only) tended to occur more often in the organic group.

The Diabetic Group

The 26 diabetic men with erectile failure were first divided into those with (n=9) and without (n=17) evidence of psychogenic factors that could account for or contribute to their erectile dysfunction. The principal results in these two groups are shown in Table 3 together with the results from the four potent diabetic men (Group DN).

The "psychogenic" group, who were slightly younger, showed a greater erectile response to fantasy, but not to film. The pulse amplitude difference during responses to film was however greater in the psychogenic group who also showed a smaller rise in systemic blood pressure to erotic stimulation.

Autonomic Neuropathy

The comparison of the groups with and without evidence of autonomic neuropathy is shown in Table 4. There were no differences between the groups in response to fantasy. In erectile response to film, group 1 was significantly more responsive than group PS & S but did not differ from group PS. Although both groups with autonomic damage (groups PS and PS & S) showed smaller pulse amplitude changes than the non-neuropathic group (group1), the differences were not significant. There was no difference between the 3 groups in terms of systemic blood pressure response.

There was a tendency for type VI responses to be more frequent amongst those with autonomic neuropathy.

Retinopathy

Comparison of the three groups with differing degrees of diabetic retinopathy is shown in Table 5. Although presence of retinopathy was associated with smaller erectile responses to film, the differences between the three groups were not significant. Penile pulse amplitude differences, however, were significantly smaller in those with severe retinopathy

(i.e. exudative or proliferative) than those without retinopathy. There were no significant differences in systemic blood pressure response.

The three groups did not differ in their response to fantasy and there was no obvious association between degree of retinopathy and type of erectile response.

DISCUSSION

These results indicate that our method of assessing sexual responsiveness has diagnostic value as well as being of psychophysiological interest. Measurement of erections to film stimuli distinguished between organic and psychogenic aetiologies as shown in the comparison of the three matched groups (N, NI, DI) and the within group comparison of the non-diabetic impotent men. Fantasy response was less effective in distinguishing between diagnostic groups.

Kockott et al (1980) have reported the only other comparable data in the literature so far. Our findings support theirs in that our diabetic impotent subjects showed smaller erectile responses than our normal controls.

The measurement of change in penile pulse amplitude has been of most relevance to the diabetic group. It did not distinguish between the non-diabetic impotent men and the normal controls, nor, within the impotent group, between those with predominantly psychogenic and organic aetiologies. However, not only was the diabetic group different from the other two in its pulse amplitude response, there were also interesting differences between sub-groups of diabetic men. The diabetic men with obvious psychogenic factors showed more normal pulse amplitude change than those with only the diabetes to account for their problem, even though they didn't differ significantly in the amount of erection produced. The relationship with

diabetic complications was also of interest. Penile pulse amplitude change was significantly smaller in those with severe retinopathy, whereas the differences between those with and without autonomic neuropathy was shown most clearly (and significantly) in the degree of erection. These two complications usually co-existed, so their effects may have confounded one another. Our results suggest, however, that retinopathy was, as one would expect, most associated with impairment of arterial inflow (as shown by pulse amplitude change). Autonomic neuropathy, on the other hand, was more associated with the degree of erection, and hence may be exerting its main effects on the neural control of venous outflow or arterio-venous shunt mechanisms. This effect on erection was only significant in the group with both parasympathetic and sympathetic damage. Whether this is due to the added effects of the sympathetic damage or to the generally more severe degree of autonomic damage in this group is not yet clear. The possibility that the parasympathetic and sympathetic damage may produce differential effects on arterial inflow to the penis is worthy of consideration. Parasympathetic damage alone might be expected to result in unopposedvasoconstrictor tone and hence smaller pulse amplitude. With added sympathetic damage, the vasoconstrictor tone would also be reduced, leading, in the presence of normal vessels, to larger but less responsive pulse amplitude. It is therefore of interest that in those three men with both parsympathetic and sympathetic damage but without severe retinopathy, there were relatively large increases in pulse amplitude for the small degree of erection produced. Obviously more evidence will be required before this interesting possibility can be assessed. If, in the presence of parasympathetic damage, unopposed vasoconstrictor tone does occur and adversely affects erection, then it may be amenable to pharmacological treatment. It is noteworthy that those diabetic impotent men with neither

retinopathy nor autonomic neuropathy all gave evidence of psychogenic causation.

The typology of erections, based on the temporal relationship between penile pulse amplitude and diameter change, remains of uncertain diagnostic significance, but there are some interesting possibilities that deserve further study. The type VI response, pulse amplitude change without diameter change, may be relevant to specific types of pathology as it was more frequent amongst the diabetics, especially those with autonomic neuropathy. This is consistent with our suggestion that neuropathy principally affects the non-arterial components of erection. Type IV responses may also prove to be of considerable interest when we have more information. They were certainly more frequent amongst the non-diabetic impotent group, but did occur in some normal and diabetic subjects. As suggested in the first paper, the temporal dissociation between pulsatile flow and penile diameter change that characterises this type of response, suggests some active inhibition or restriction of the arterial component during response to an erotic stimulus. This may be a manifestation of performance anxiety, in which case we should expect to find it occurring not only in those with psychogenic impotence but also in some normal subjects as well as some with organic aetiologies. If so, it would be of considerable theoretical interest as well as diagnostic significance. Our method of assessing this temporal relationship has so far been crude, but we believe that these preliminary findings justify a further investigation of this phenomenon with more sophisticated methods of data analysis.

The diagnostic value of our method of assessment needs to be compared with other methods to establish its proper place in clinical practice. A comparison of erectile responses assessed by this method with those recorded during sleep will be reported in a further paper (Shapiro, O'Carroll & Bancroft).

Our results suggest that small vessel disease, autonomic neuropathy and psychogenic factors may all contribute to the erectile problems of diabetic men, possibly by affecting different components of the erectile process. This method of investigation should lead to a greater understanding of these mechanisms.

TABLE 1

PSYCHOPHYSIOLOGICAL RESPONSES TO EROTIC FILM AND FANTASY - COMPARISON OF 3 GROUPS OF MEN

		Normal (N) n=19	Non-Diabetic Impotence (NI) n=19	Diabetic Impotence (DI) n=19	Analysis of variance (d.f.2,54)
Mean Max. Erection to film (mm/increase/diam.)	Mean S.D.	9.3 ±2.9	8.3 ±5.3	4.2 ±4.1	F=7.65 p=<0.005 N v DI p=<0.005 NI v DI p=<0.05
Mean Max. Erection to fantasy (mm/increase/diam.)	Mean S.D.	4.4 ±4.2	2.7 ±2.2	0.8 ±0.9	F=7.72 p=<0.05 N v DI p=<0.001
Penile Pulse Amplitude Mean Baseline μV	Mean S.D.	702 ±531	525 ±252	419 ±354	F=3.78 p=<0.05 N v DI p=<0.05
'Difference' in response to fantasy μV	Mean S.D.	1188 ±1250	876 ±715	346 ±354	F=9.22 p=<0.001 N v DI p=<0.001 NI v DI p=<0.01
'Difference' in response to film μV	Mean S.D.	1729 ±1431	1061 ±1212	474 ±449	F=7.87 p=<0.005 N v NI p=<0.1 N v DI p=<0.005
Systemic Blood Pressure	Mean (S.D.)				
Mean Baseline	Systolic Diastolic	118.1 (14.6) 75.7 (11.4)	124.1 (15.3) 77.8 (13.2)	131.3 (23.0) 81.6 (13.1)	
Response to film	Systolic Diastolic	+25.0 (11.4) +17.5 (9.8)	+19.5 (7.5) +13.2 (7.1)	+24.3 (10.5) +15.6 (7.3)	N.S.
Response to fantasy	Systolic Diastolic	+16.3 (8.6) +15.1 (9.9)	+12.4 (5.7) + 9.8 (5.6)	+13.7 (6.0) +10.6 (6.1)	

TABLE 2

COMPARISON OF NON-DIABETIC SEXUALLY DYSFUNCTIONAL MEN WITH PREDOMINANTLY 'PSYCHOGENIC' AND ORGANIC AETIOLOGIES

		Age	Erectile Response mm. inc. diam.		Penile Pulse Amplitude Difference μV		Systemic Blood Pressure mm Hg			
							Baseline		Response to Film	
			To Fantasy	To Film	To Fantasy	To Film	Systolic	Diastolic	Systolic	Diastolic
'Psychogenic' Group n = 17	Mean (S.D.)	37.7 (11.0)	1.61 (1.85)	8.81 (5.1)	822 (681)	1269 (1220)	119.7 (8.5)	75.8 (10.2)	+18.5 (7.3)	+13.2 (7.3)
'Organic' Group n = 8	Mean (S.D.)	46.4 (11.2)	0.51 (0.51)	2.5 (1.5)	781 (625)	819 (512)	134.7 (18.9)	78.8 (18.4)	+23.7 (7.4)	+13.6 (4.4)
t-test		N.S.	N.S.	t=3.38 p=<0.005	N.S.	N.S.	t=2.73 p=<0.002	N.S.	N.S.	N.S.

TABLE 3

COMPARISON OF DIABETIC MEN WITHOUT IMPOTENCE AND THOSE WITH AND WITHOUT PSYCHOGENIC CAUSES FOR THEIR IMPOTENCE

		Age	Erectile Response mm. inc. diam.		Penile Pulse Amplitude Difference μV		Systemic Blood Pressure mm Hg			
							Baseline		Response to Film	
			To Fantasy	To Film	To Fantasy	To Film	Systolic	Diastolic	Systolic	Diastolic
Non-impotent Diabetic Men n = 4	Mean (S.D.)	38.5 (13.3)	5.16 (3.7)	10.36 (1.5)	667 (286)	847 (326)	116.6 (8.2)	78.7 (3.9)	+22.9 (4.0)	11.4 (2.0)
Diabetic Psychogenic Group n = 9	Mean (S.D.)	38.3 (9.9)	1.49 (1.48)	5.5 (4.0)	471 (434)	992 (549)	130.1 (17.3)	74.2 (6.8)	+18.1 (11.3)	+12.0 (4.5)
Diabetic Non-Psychogenic Group n = 17	Mean (S.D.)	43.2 (7.7)	0.63 (0.6)	3.56 (2.9)	262 (203)	386 (309)	137.1 (23.4)	88.0 (14.8)	+28.2 (9.7)	+18.6 (8.3)
t-test (Impotent Groups Only)		N.S.	t=1.8 p=<0.1	N.S.	N.S.	t=3.06 p=<0,01	N.S.	t=2.34 p=<0.05	t=2.15 p=<0.05	t=1.94 p=<0.1

TABLE 4

COMPARISON OF DIABETIC MEN WITH AND WITHOUT AUTONOMIC NEUROPATHY

Impotent Diabetic Men		Age	Erectile Response to Film mm. incr. diam.	Penile Pulse Amplitude Difference to Film μV mm. incr. diam.	Systemic Blood Pressure mm Hg			
					Baseline		Response to Film	
					Systolic	Diastolic	Systolic	Diastolic
Group 1								
Normal cardiovascular n = 6	Mean (S.D.)	40.0 (7.6)	6.2 (3.8)	1043 (579)	136.4 (16.0)	83.5 (16.1)	+26.7 (11.0)	+19.2 (8.1)
Group PS								
Parasympathetic Damage Only n = 13	Mean (S.D.)	42.4 (9.2)	4.8 (3.1)	537 (417)	138.8 (23.9)	84.0 (13.6)	+24.6 (13.2)	+15.3 (8.6)
Group PS + S								
Parasympathetic and sympathetic damage n = 7	Mean (S.D.)	42.0 (8.6)	1.6 (1.6)	322 (308)	123.4 (17.2)	84.7 (15.5)	+23.3 (7.0)	+16.4 (7.5)
Anovar		N.S.	F=4.3 p=<0.05 I v PS + S p=<0.05	F=3.37 p=<0.1	N.S.	N.S.	N.S.	N.S.

TABLE 5

COMPARISON OF DIABETIC MEN WITH DIFFERENT DEGREES OF RETINOPATHY

	Age	Erectile Response to Film mm. incr. diam.	Penile Pulse Amplitude Difference to Film μV mm. incr. diam.	Systemic Blood Pressure mm Hg			
				Baseline		Response to Film	
				Systolic	Diastolic	Systolic	Diastolic
1. No Retinopathy (NR) n = 8 Mean	44.4	5.95	965	135.5	77.3	+25.9	+15.6
(S.D.)	(8.4)	(3.7)	(587)	(15.0)	(7.6)	(13.0)	(4.3)
2. Background Retinopathy (BR) n = 9 Mean	41.3	4.2	490	141.8	90.1	+27.8	18.5
(S.D.)	(9.1)	(3.6)	(329)	(14.7)	(16.0)	(11.2)	(10.6)
3. Exudative or Proliferative Retinopathy (EPR) n = 8 Mean	39.4	2.7	282	128.9	84.2	+22.4	+15.5
(S.D.)	(8.5)	(2.5)	(291)	(31.9)	(14.6)	(9.8)	(7.6)
4. Anovar	N.S.	N.S.	F=5.25 p=<0.025 NR v EPR p=<0.025	N.S.			

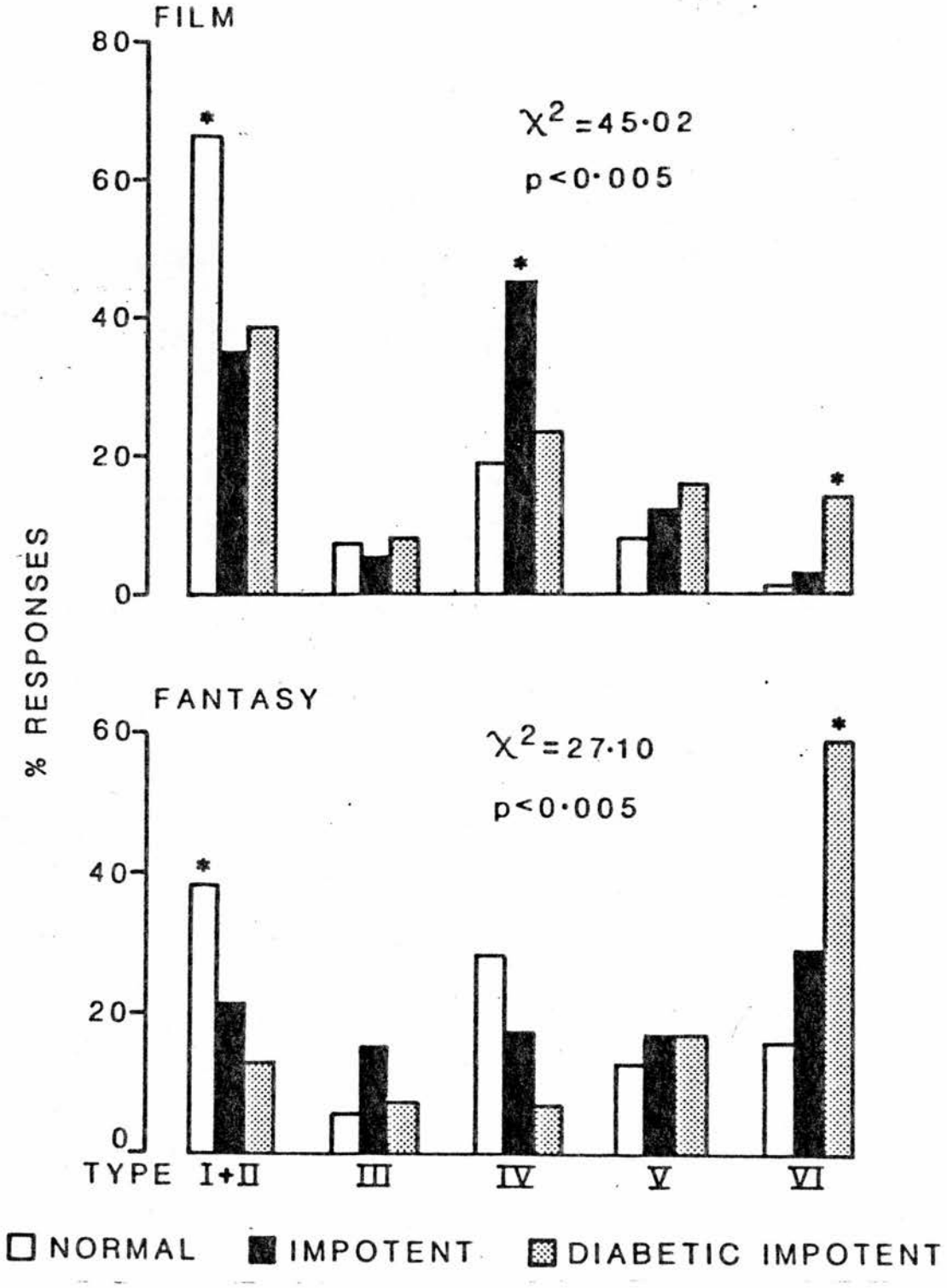


FIGURE 1. Distribution of six types of erectile response to erotic film and fantasy in the three groups of subjects. (For definition of types, see text and Paper 1.) Percentages shown are of all responses within each group.

APPENDIX C

Published articles derived from these research studies.

Diabetologia 18, 279–283 (1980)

Diabetologia

The Prevalence of Diabetic Impotence

D. K. McCulloch, I. W. Campbell, F. C. Wu, R. J. Prescott, and B. F. Clarke

Diabetic and Dietetic Department, Royal Infirmary, and Medical Computing and Statistics Unit, Edinburgh University, Edinburgh, Scotland

Summary. In a survey of 541 diabetic males, aged 20–59 years, 190 (35%) had erectile impotence. Using linear logistic regression models for analysis the five most significant associations with impotence were age ($p < 0.001$), treatment with either insulin or oral hypoglycaemic agents ($p < 0.001$), retinopathy ($p < 0.001$), symptomatic peripheral neuropathy ($p < 0.001$) and symptomatic autonomic neuropathy ($p < 0.005$). The greatest correlations were found in patients with severe microangiopathy, as demonstrated by proliferative retinopathy and symptomatic autonomic neuropathy. In addition the duration of diabetes and the presence of ischaemic heart disease, nephropathy and poor diabetic control may also be associated with diabetic impotence. It is concluded that diabetic impotence is still a common problem and may have a multifactorial aetiology.

Key words: Diabetic impotence, prevalence, aetiological factors.

The increased frequency of impotence in the diabetic male has long been recognised [7]. Despite improvement in the treatment of diabetes since the early insulin era there has been no decrease in recent reports of the frequency of diabetic impotence [7, 10, 14]. Thus the prevalence of impotence with increasing age in diabetic men aged between 20–60 years is still approximately 18–71% [19] and considerably greater than 0.1–18.4% for the corresponding normal male population [13].

There has been no previous extensive survey of the prevalence of diabetic impotence in the United Kingdom. The aim of the present study was therefore to ascertain the prevalence in males attending a large U. K. diabetic clinic. An assessment was also made of possible contributing factors involved in the aetiology of diabetic impotence.

Materials and Methods

During a nine month period 563 males attending the Diabetic Out-Patient Department were interviewed. A total of 132 clinics were covered and at each clinic every male aged between 20–59 years was included. After three months an initial non-randomised group of 319 men (Group 1) had been interviewed. At this time it was decided to interview a random group of approximately 100 men to exclude the possibility of bias in the original group. The total clinic male population aged 20–59 years was 887 and from the remaining 568, a random sample of 101 men (Group 2) was drawn who were subsequently interviewed over a six month period. Over this latter period a second non-random group of 121 men (Group 3) who were attending the clinic and not included in the random sample were also interviewed.

The total number of men included for study was thus 541, representing 61% of the male clinic population aged between 20–59 years. A further 22 who were unable to give satisfactory interviews were omitted: in the two non-random groups (Groups 1 and 3) 9 were mentally defective, 2 had cerebrovascular accidents with dysphasia and 2 were unable to speak English; in the random group (Group 2) 5 had recently left the area, 1 was hospitalised elsewhere, 2 were mentally defective and 1 had a cerebrovascular accident.

A detailed questionnaire was completed and included the patient's age, weight and standard weight (Metropolitan Life Insurance Company Tables, 1959), age at onset of diabetes and marital status. Diabetic treatment was recorded as diet alone, oral hypoglycaemic agents or insulin. Enquiry was made of other drug therapy, angina pectoris, previous myocardial infarction or cardiac failure, intermittent claudication, thyroid dysfunction, previous sympathectomy or other abnormality that might predispose to organic impotence such as neurological disease or previous injury. A note was taken of the average weekly quantity of alcohol consumed by each patient.

All patients had a retinal examination at least yearly with both pupils dilated and retinopathy status was recorded as none, background, exudative (or maculopathy) or proliferative, many of the latter having had or were awaiting photocoagulation treatment. The presence of nephropathy was indicated from several urinal-

0012-186X/80/0018/0279/$01.00

yses over the previous 12 months using "Albustix" and the proteinuria recorded as none (0), intermittent (0/+), moderate (++) or heavy (+++).

Careful enquiry was made of symptoms suggestive of peripheral neuropathy (numbness, parasthesiae, burning pains and limb weakness).

These individual features were graded as "mild/moderate" or "severe". Objectively, those with mild/moderate complaints usually had documented in their case records absent ankle jerks, absent vibration sense at the ankle, diminished sensation in the feet and/or muscle wasting. Those with severe symptoms generally had more extensive sensory loss in the lower limbs, absent knee jerks and often had evidence of recent or old neuropathic ulceration. The criteria for the presence of symptomatic peripheral neuropathy were one or more severe or two or more mild/moderate symptoms along with objective evidence (as outlined above) that these symptoms were due to neuropathy.

Enquiry was also made of symptoms of autonomic neuropathy (postural hypotension, intermittent diarrhoea especially nocturnally, epigastric fullness, bladder dysfunction, diminished sweating in the legs, gustatory sweating and hypoglycaemic unawareness). The criteria for the presence of symptomatic autonomic neuropathy were two or more severe or three or more mild/moderate features. All such patients had well defined objective evidence of autonomic neuropathy from previous studies [8, 2]. Diabetic control was assessed by taking the average of the last six 2 h post prandial glucose estimations at previous clinic visits or all the 2 h post prandial glucose values excluding the initial reading if the patient had only been attending for a short time. Three groups of diabetic control were arbitrarily designated:

Good – mean blood glucose level less than 9 mmol/l;
Fair – 9.1–13.9 mmol/l;
Bad – 14.0 mmol/l or greater.

The patient was also asked if he was able to obtain a normal penile erection and impotence was regarded as present if there had been partial or complete failure to obtain an erection for at least six months. The duration of impotence was recorded in months. If the patient was potent at the time of interview, enquiry was made if transient impotence had ever been present in the past, e. g. during anxiety or poor control. Such patients were entered in the study as being potent. Any decrease in libido was noted and enquiry was made for features suggestive of a psychological cause for the impotence [4].

The information was recorded on a questionnaire form, coded and transferred to punch cards. Using the Edinburgh Regional Computing Centre's facilities the computer package SPSS was used for the production of the tables. In the tabulations which follow three age groups were chosen to give adequate numbers in each group – 20–34 years, 35–49 years, 50–59 years. Patient Groups 1, 2 and 3 were compared using Chi-squared tests or a one-way analysis or variance dependent upon whether the variable concerned was qualitative or quantitative.

Investigation of the association of various clinical features with impotence involved the use of linear logistic models which were fitted using a second computer package, Genstat. The use of such models is well described by Cox [5]. They allow the probability of impotence to be related to a set of clinical variables simultaneously. In this way the interrelationship of the variables can be taken into account and the relative importance of the variables in producing impotence can be assessed. The method has considerable similarities to methods of multiple regression, which are well described by Armitage [1].

Table 1. Relationship of age to impotence in diabetic males

Age range (years)	Total no. diabetics	No. impotent	% impotent
20–24	53	3	5.7
25–29	35	5	14.3
30–34	44	7	15.9
35–39	43	13	30.2
40–44	52	15	28.8
45–49	91	33	36.3
50–54	99	49	49.5
55–59	124	65	52.4
Total	541	190	35.1%

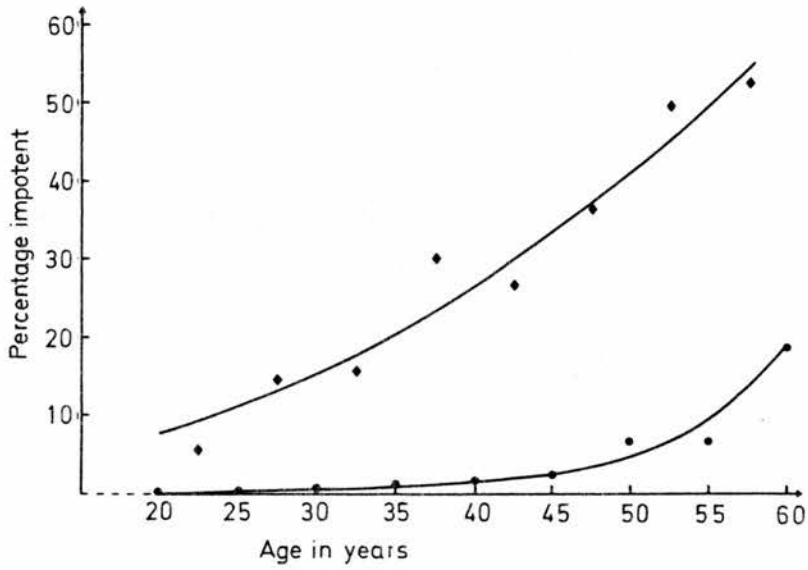


Fig. 1. Relationship of impotence to age in diabetic and normal male subjects. The normal male data are derived from Kinsey et al. [13].
●——● Normal, ◆——◆ Diabetics

Table 2. Relationship of duration of diabetes to impotence in insulin dependent and insulin independent males within three age groups

	Insulin dependent diabetics age (years)			Insulin independent diabetics age (years)		
Duration (years)	20–34	35–49	50–59	20–34	35–49	50–59
0– 4	5% (2/40)	18% (2/11)	33% (3/9)	0/6	16% (9/58)	35% (26/75)
5–14	16% (10/61)	38% (15/40)	50% (13/26)	0/1	53% (9/17)	50% (28/56)
15–29	13% (3/24)	44% (20/45)	79% (26/33)	–	0/2	63% (5/8)
30+	–	46% (6/13)	81% (13/16)	–	–	–

Results

Comparison of the non-randomised groups (1 and 3) and the randomised group (2) were made. The differences between the groups are outlined below. There were few significant differences and they were such that the amalgamation of the grouped data would give valid results on diabetic impotence. The ages of the three groups were comparable with mean ± S. E. M. of group 1, 2 and 3 being 43.4 ± 0.6, 46.1 ± 1.1 and 43.7 ± 1.1 respectively. The overall prevalence of impotence was 35%, 39% and 31% respectively in the three groups. The only variables demonstrating significant differences between the groups at the 5% level were retinopathy with prevalences of 34%, 22% and 26% respectively and symptomatic peripheral neuropathy with prevalences of 23%, 13% and 14% in the three groups. All subsequent analyses were therefore performed with the combined data from all three groups, treating this as if it were a random sample from the clinic population.

Of the 541 men interviewed, 190 (35%) were impotent (Table 1). The increasing prevalence of impotence with age is shown in the figure and over the age range studied this relationship can be described adequately by a logistic curve.

The effect of duration of diabetes on the prevalence of impotence within the three age groups is shown in Table 2. There was an increasing prevalence of impotence with increasing duration of diabetes in all age groups but no difference in prevalence was seen between the insulin dependent and insulin independent groups.

Two hundred and eighty (80%) of the potent and 173 (91%) of the impotent subjects were married. Libido was diminished in 29 (8.3%) of the potent diabetics and in 53 (28%) of the impotent diabetics. In the latter none had features suggestive of psychogenic impotence and it may be that the diminished libido was secondary to the impotence. Transient impotence had occurred in 24 of the potent subjects, 8 during poor control, 4 during anxiety and 12 at other times such as at diagnosis of diabetes (3 subjects), following excessive alcohol (2 subjects) and during intercurrent unrelated illnesses such as myocardial infarction.

Table 3. Relationship of diabetic treatment, retinopathy, peripheral and autonomic neuropathy to impotence within three age groups

	Age (years)		
Variable	20–34	35–49	50–59
Treatment			
Insulin	12% (15/125)	39% (43/109)	65% (55/84)
Oral agents[a]	0% (0/3)	35% (13/37)	56% (43/77)
Diet	0% (0/4)	13% (5/40)	26% (16/62)
Retinopathy			
None	5% (5/96)	24% (29/120)	39% (63/162)
Background	10% (2/20)	34% (12/35)	74% (26/35)
Exudative	0% (0/4)	46% (6/13)	94% (16/17)
Proliferative	67% (8/12)	78% (14/18)	100% (9/9)
Peripheral neuropathy			
Absent	7% (8/116)	27% (44/151)	44% (75/169)
Present	44% (7/16)	57% (20/35)	72% (39/54)
Autonomic neuropathy			
Absent	9% (11/127)	30% (54/179)	49% (104/213)
Present	80% (4/5)	100% (7/7)	100% (10/10)

[a] Within the group of patients on oral hypoglycaemic agents there was no difference in impotence in each age group in those taking sulphonylureas or biguanides (metformin)

Using the linear logistic model five variables showed a significant association with impotence: age ($p < 0.001$), treatment of diabetes with insulin or oral hypoglycaemic agent but not diet alone ($p < 0.001$), retinopathy ($p < 0.001$), symptomatic peripheral neuropathy ($p < 0.001$) and symptomatic autonomic neuropathy ($p < 0.005$). A summary of the effects of these latter four variables is shown in Table 3 within the three age groups. Impotence was seen in all patients aged 50 years or more with proliferative retinopathy and in those aged 35 or more with autonomic neuropathy.

The presence of ischaemic heart disease, nephropathy and poor diabetic control may also be

Table 4. Relationship of nephropathy, control of diabetes and ischaemic heart disease to impotence within three age groups

Variable	Age (years)		
	20–34	35–49	50–59
Nephropathy[a]			
None (0)	7% (8/109)	28% (43/155)	47% (93/196)
Intermittent (0/+)	18% (2/11)	44% (8/18)	68% (13/19)
Moderate (++)	40% (4/10)	63% (5/8)	100% (4/4)
Heavy (+++)	50% (1/2)	100% (5/5)	100% (4/4)
Control[a]			
Good	7% (2/29)	21% (13/61)	34% (25/74)
Fair	9% (5/53)	28% (21/75)	54% (53/98)
Poor	16% (8/50)	54% (27/50)	71% (36/51)
Ischaemic heart disease			
Absent	11% (15/132)	33% (54/166)	48% (83/174)
Present	–	35% (7/20)	63% (31/49)

[a] Nephropathy and control are defined in the patients and methods section

Table 5. A review of studies outlining the prevalence of impotence in diabetic men

Reference	Number of diabetics	% impotent
21	198	55
23	314	51
17	436	52
20	350	75
19	146	43
7	200	59
10	299	40
14	175	49
Present study	541	35

associated with diabetic impotence (Table 4). However, these latter variables are closely associated with the other risk factors and so statistical significance is only achieved at the 10% level. Likewise, duration of diabetes was not found to have a statistically significant association with the prevalence of impotence when analysed using the linear logistic regression model. This occurs despite its obvious aetiological importance, because its effect on the model is indirect. Duration of diabetes is associated with an increasing prevalence of many other aetiological factors such as microangiopathy and neuropathy and so its individual importance is not considered to be significant in the context of the analysis using the linear logistic model.

Discussion

In our study the prevalence of impotence (35%) is the lowest so far reported compared with other recent surveys from USA, Europe and South America (Table 5). We have studied the largest number of patients, aged 20–59 years, but otherwise unselected as regards treatment, duration or complications. In addition the study was conducted over a nine month period to include less frequent attenders at the clinic. Our method of selection thus ruled out some of the bias in selection present in previous studies. Although impotence as in non-diabetics increases with age, in our survey 76 (24%) of those less than 50 years were impotent.

In the survey impotence was defined as the inability to initiate and sustain a satisfactory penile erection. Penile erection occurs as a reflex mediated by the parasympathetic nerve fibres from the spinal cord segments sacral 2–4 (nervierigentes). It is generally assumed that diabetic impotence is due solely to autonomic neuropathy affecting these nerves. This is mainly based on indirect evidence that impotence is associated with both anatomical [9] and physiological abnormalities [6] of the bladder in some of these diabetics. There has been one unconfirmed study showing alterations in the autonomic nerve fibres in the corpora cavernosa in impotent diabetics [11], again suggesting that a neurological lesion could cause the impotence.

However, in our previous studies of autonomic neuropathy we have shown that impotence can frequently occur alone without any of the other symptom-complexes of autonomic neuropathy and in such patients cardiovascular reflexes such as the Valsalva manoeuvre and the blood pressure response to sustained handgrip are normal [8] as is the plasma renin response to standing [3] as well as the preservation of normal testicular sensation [2]. There is now agreement that there is no obvious endocrine abnormality causing diabetic impotence and normal gonadotrophin levels [10], normal testosterone concentrations [14] and a normal gonadotrophin response to LH-RH stimulation [25] have been reported. It has become clear to those dealing with diabetic impotence that in some cases there would appear to be many disease processes such as psychogenic, neurological and vascular disorders involved in the aetiology of impotence, an idea suggested in 1950 by Simpson [24]. Although psychogenic factors are the commonest cause of non-diabetic impotence, we have been impressed by how infrequently any of the diabetic males had features to suggest psychogenic cause [4].

That impotence in normal males [13] and in diabetics [21] increases with age is well recognised.

The significant association of impotence with diabetics on oral agents and insulin rather than diet alone differs from previous studies where impotence occurred equally in patients on all forms of therapy [23, 17]. Our results suggest that impotence may be associated with an increased tendency to microangiopathy. The strong correlation with the presence and severity of retinopathy has not been shown by others. In the smaller study of Rubin and Babbott [21] retinopathy occurred with equal frequency in both potent and impotent diabetics. The association of impotence with neuropathic symptoms is not unexpected. There are many previous studies to show that impotence is found in a high percentage of patients with peripheral neuropathy [22, 16] and with autonomic neuropathy [7, 9].

An association with ischaemic heart disease was found at the 10% level but no significant association was found with the presence of intermittent claudication. A prerequisite for normal erection is an adequate blood supply to the genital region as seen by the occurrence of impotence in the Leriche syndrome [15]. Rubin and Babbott [21] found an equal incidence of vascular disorders in their potent and impotent diabetics. In an unconfirmed angiographic study in impotent diabetics Fournier and Huguet [12] have claimed an absence of blood supply to the corpora cavernosa of the penis. However, more extensive investigations of penile blood supply have not been carried out.

There are many variables therefore in the aetiology of diabetic impotence. Although it is possible to identify the predominant cause in some patients, detailed investigations of subgroups of impotent patients will be necessary to clarify the problem further.

Acknowledgement. We are most grateful for the help of Mrs. Sarah Dickson in the Diabetic Department, Royal Infirmary of Edinburgh and Wilma Hepburn in the Medical Computing and Statistics Unit, for their help in the preparation of this paper.

References

1. Armitage P (1971) Multiple regression and multivariate analysis. In: Statistical methods in medical research. Blackwell, Oxford, p 302–348
2. Campbell I W, Ewing D J, Clarke B F, Duncan L J P (1974) Testicular pain sensation in diabetic autonomic neuropathy. Br Med J II: 638–639
3. Campbell I W, Ewing D J, Anderton J L, Thompson J H, Horn D B, Clarke B F (1976) Plasma renin activity in diabetic autonomic neuropathy. Eur J Clin Invest 6: 381–385
4. Cooper A J (1972) Diagnosis and management of "endocrine impotence". Br Med J II: 34–36
5. Cox D R (1970) The linear logistic model. In: Analysis of binary data. Methuen, London, p 14–29
6. Ellenberg M, Weber H (1967) The incipient asymptomatic diabetic bladder. Diabetes 16: 331–335
7. Ellenberg M (1971) Impotence in diabetes: the neurologic factor. Ann Intern Med 75: 213–219
8. Ewing D J, Campbell I W, Burt A A, Clarke B F (1973) Vascular reflexes in diabetic autonomic neuropathy. Lancet II: 1354–1356
9. Faerman I, Maler M, Jadzinsky M, Alvarez E, Fox D, Zilbervarg J, Cibeira J B, Colinas R (1971) Asymptomatic neurogenic bladder in juvenile diabetics. Diabetologia 7: 168–172
10. Faerman I, Vilar O, Rivarola M A, Rosner J M, Jadzinsky M N, Fox D, Perez Loret A, Bernstein-Hahn L, Saraceni D (1972) Impotence and diabetes. Studies of androgenic function in diabetic impotent males. Diabetes 21: 23–30
11. Faerman I, Glocer L, Fox D, Jadzinsky M N, Rapaport M (1974) Impotence and diabetes. Histological studies of the autonomic nervous fibres of the corpora cavernosa in impotent diabetic males. Diabetes 23: 971–976
12. Fournier A M, Huguet J F (1968) Vascularisation du bulbe caverneux. Aspect normal et pathologique (cas particulier du diabète). J Radiol Electr Med Nucl 49: 515–518
13. Kinsey A C, Pomeroy W B, Martin C E (1948) Age and sexual outlet. In: Sexual behaviour in the human male. Saunders, Philadelphia, p 218–262
14. Kolodny R C, Kahn C B, Goldstein H H, Barnett D M (1974) Sexual dysfunction in diabetic men. Diabetes 23: 306–309
15. Leriche R (1940) De la résection du carrefour aortico-iliaque avec double sympathectomie lombaire pour thrombose artéritique de l'aorte; le syndrome de l'obliteration terminoaortique par artérite. Presse Med 48: 601–604
16. Martin M M (1953) Involvement of autonomic nerve-fibres in diabetic neuropathy. Lancet I: 560–565
17. Montenero P, Donatone E (1962) Diabète et activité sexuelle chez l'homme. Diabete 10: 327–335
18. Neubauer M, Demisch K, Schöffling K, Wiegelmann W, Salbach H G (1971) Andrologische Untersuchungen, Testosteronspiegel im Plasma und Choriongonadotropin – Belastungen bei Diabetikern mit Potenzstörungen. Verh Dtsch Ges Inn Med 77: 1060–1063
19. Neubauer M, Schöffling K (1977) Sexualstörungen bei diabetischen Männern. In: Oberdisse K (ed) Handbuch der inneren Medizin, 7/2B: Diabetes Mellitus. Springer, Berlin Heidelberg New York, p 465–505
20. Prikhozhan, V M (1967) Impotence in diabetes mellitus. Probl Endokrinol (Mosk) 13: 37–41
21. Rubin A, Babbott D (1958) Impotence and diabetes mellitus. J A M A 168: 498–500
22. Rundles R W (1945) Diabetic neuropathy; general review with report of 125 cases. Medicine (Baltimore) 24: 111–160
23. Schöffling K (1960) Störungen der Keimdrüsenfunktion bei männlichen Zuckerkranken. Beitr. Sexualforsch 19: 1–83
24. Simpson S L (1950) Impotence. Br Med J I: 692–697
25. Wright A D, London D R, Holder G, Williams J W, Rudd B T (1976) Luteinizing release hormone tests in impotent diabetic males. Diabetes 25: 975–977

Received: January 23, 1979,
and in revised form: October 5, 1979

Dr. D. K. McCulloch
Diabetic and Dietetic Department
Royal Infirmary
Edinburgh EH3 9YW
Scotland

Reprinted from DIABETES CARE, VOL. 3, NO. 2, MARCH-APRIL 1980

Effect of Alcohol Intake on Symptomatic Peripheral Neuropathy in Diabetic Men

DAVID K. McCULLOCH, IAN W. CAMPBELL, ROBIN J. PRESCOTT, AND BASIL F. CLARKE

In a group of 541 white diabetic men aged 20–59 yr attending one clinic it was found that 91 (15%) drank heavily, while a further 39 (7%) had frank alcoholism. The prevalence of symptomatic peripheral neuropathy was much higher in the 120 men who drank excessively. It is considered important, therefore, when treating diabetic patients with peripheral neuropathy not to assume that the diabetes itself is the cause in all cases. The alcoholic intake of the patient should be ascertained and, if excessive, it should be pointed out to the patient that this may well be the predominant factor causing symptoms.
DIABETES CARE 3: 245–247, MARCH–APRIL 1980.

Most diabetic patients are advised to drink alcohol in moderation only and to restrict this to diabetic beer and lager or spirits without sweetened additives. Krall and Joslin[1] urged complete abstention, and although others are more liberal in attitude,[2] most agree that regular ingestion of alcohol is not to be encouraged among diabetic individuals, and that it may lead to weight gain. Our own policy has been to accept a moderate alcohol intake (up to 10 alcoholic drinks per week) but to discourage any more alcohol than this.

Although diabetes and alcohol are well-known individual factors causing peripheral neuropathy, little attention has been paid to the effect of alcohol intake on peripheral neuropathy among diabetic individuals. This present study examines the extent to which patients follow advice about alcohol intake and whether this affects neurologic complications in these patients.

PATIENTS AND METHODS

During a 9-mo period 541 men were interviewed, representing 61% of the male clinic population aged between 20 and 59 yr (mean age 44.0 ± 11.6 yr). These comprised all such men attending 134 routine clinics during this period and included a random sample of 101 men. Male patients only were selected because this study was part of a larger review of the male clinic population to ascertain the prevalence of impotence.[3] It was possible to check from the random sample that there was no important bias in the selection of the other 440 patients. A questionnaire was completed at the interview and a note made of the patient's weight, standard weight (Metropolitan Life Insurance Company Tables, 1959), and diabetic treatment (diet alone, oral hypoglycemic agents, or insulin). The diet in nonobese non-insulin-dependent diabetic patients, whether on oral agents or not, was a simple carbohydrate-restricted diet (40% carbohydrate, 45% fats, 15% protein), while obese non-insulin-dependent diabetic patients were on a calorie-restricted diet (generally 500–1000 cal), often along with metformin. Those on insulin received a carbohydrate exchange diet, using 10-g carbohydrate exchanges, and on average took 240 g of carbohydrate daily. No patient was on any particular vitamin supplement. Enquiry was made of any drugs the patients were receiving that might contribute to the presence of peripheral neuropathy.[4]

A history of alcohol intake was obtained and graded as: grade 1 ("nondrinkers"), men who were nondrinkers or took less than six alcoholic drinks throughout the year, usually limited to special occasions; grade 2 ("social drinkers"), those who consumed generally up to 10 alcoholic drinks per week, usually on two or three nights plus occasional wine with a meal; grade 3 ("heavy drinkers"), those taking up to three to four drinks almost every night and often more at weekends; and grade 4 ("alcoholic"), patients with drinking habits frankly outside the social norm and those attending, previously or at present, the alcoholic treatment center in the city. Many of these patients drank half a bottle of spirits or more per day.

Although there appears to be a gap between grades 2 and 3, this was not found to be the case. These four grades represent distinct drinking patterns occurring in the Scottish population under study. There is a clear cutoff between those

TABLE 1
Effect of alcohol intake and duration of diabetes on prevalence of symptomatic peripheral neuropathy

Duration of diabetes (yr)	Alcohol intake	
	Moderate	Excessive
0–4	12/142* (8%)	18/57 (32%)
5–9	13/96 (14%)	11/25 (44%)
10–14	9/62 (15%)	7/18 (39%)
>14	27/121 (22%)	7/20 (34%)
Total	61/421 (14%)	43/120 (36%)

* Note: The figures represent the number of patients with symptomatic peripheral neuropathy divided by the total number of patients who fell within that alcohol intake grade and duration of diabetes. This fraction is then represented by a percentage in parentheses.

whose intake was grades 3 and 4. For this reason much of the subsequent analysis compares the moderate drinkers (grades 1 and 2) with the excessive drinkers (grades 3 and 4).

In all cases the patient's drinking pattern had been the same for more than 5 yr. Note was taken of the type of alcoholic beverage preferred, whether beer, lager, wine, or spirits.

Careful enquiry was made of symptoms suggestive of peripheral neuropathy (numbness, parasthesiae, burning pains, or limb weakness). These individual features were graded as "mild/moderate" or "severe." Objectively, those with mild/moderate complaints usually had documented in their case records absent ankle jerks, absent vibration sense at the ankle, diminished sensation in the feet, and/or muscle wasting. Those with severe symptoms generally had more extensive sensory loss in the lower limbs, absent knee jerks, and often had evidence of recent or old neuropathic ulceration. The criteria for the presence of symptomatic peripheral neuropathy was one or more severe or two or more mild/moderate symptoms along with objective evidence (as outlined above) that these symptoms were due to neuropathy.

The recorded information was coded, punched, and verified and the SPSS computer package used to produce tables.

The statistical tests of significance applied in this study are for the most part standard (Student's t tests, χ^2 tests). However, in Table 1, Woolf's test[5] was first used to test whether the relative risk of symptomatic peripheral neuropathy in patients with a high alcohol intake changed with the duration of diabetes. The significance of the effect of alcohol on symptomatic peripheral neuropathy was assessed using a test described by Cox[6] to combine the information from four separate 2 × 2 contingencies corresponding to differing durations of diabetes, while the effect of duration itself was assessed by another test described by Cox.[7]

RESULTS

It was found that 421 subjects (78%) were moderate drinkers (125 were grade 1 and 296 were grade 2) while 120 subjects (22%) were excessive drinkers (81 were grade 3 and 39 were grade 4).

Of the diabetic subjects on diet alone, the average weight of the moderate drinkers was 183 ± 3 lb and of the excessive drinkers 183 ± 5 lb. Moderate drinkers on oral hypoglycemic agents had an average weight of 163 ± 2 lb, while those who drank excessively had an average weight of 162 ± 3 lb. Among the insulin-dependent diabetic subjects, the moderate drinkers had an average weight of 158 ± 1 lb, while the excessive drinkers had an average weight of 156 ± 2 lb. Overall, 23% of the moderate drinkers were greater than 10% above standard weight compared with 30% of those who drank excessively. None of these results is statistically significant.

None of the patients with symptomatic peripheral neuropathy were found to be taking any drugs that would significantly contribute to their symptoms.

The effect of alcohol intake together with duration of diabetes on the prevalence of symptomatic peripheral neuropathy is shown in Table 1. Both these factors affected neuropathic symptoms independently, with no evidence of interaction (Woolf's test, $P > 0.4$). Neuropathic symptoms become more common the longer the patients had had diabetes ($P < 0.001$), and for any duration of diabetes the prevalence of symptomatic peripheral neuropathy was increased in those who drank excessively ($P < 0.001$). This increase was most marked in patients with a short duration of diabetes. The prevalence of neuropathic symptoms in patients who had had diabetes for less than 5 yr was increased fourfold in those who drank excessively (8% among moderate drinkers, rising to 32% among excessive drinkers). This difference became less marked the longer the patients had had diabetes. With a duration of 15 yr or more, the effect of excessive alcohol intake only increased the prevalence of neuropathic symptoms by 1½ times (22% among moderate drinkers, rising to 34% in those who drank excessively).

DISCUSSION

The effect of diabetes together with alcohol on peripheral neuropathy has not been reported previously. The occurrence of peripheral neuropathy among alcoholics is thought to be largely due to associated deficiencies of B-group vitamins, which causes damage to the axon itself.[8] Diabetes, on the other hand, causes damage to nerves primarily by a metabolic disturbance resulting in segmental demylination and axonal degeneration.[9] It may be that the combined insult to the neurons in this way may have a cumulative effect, producing more severe symptoms. That excessive alcohol seems to exert a greater influence on neuropathic symptoms among recently diagnosed diabetic persons may merely reflect the fact that, with the passage of time, pure diabetic neuropathy becomes more pronounced, such that the damaged nerves are less influenced by the effect of excessive alcohol.

The authors believe that this study is important in the assessment and treatment of symptomatic peripheral neurop-

athy in diabetes. This is a very difficult area of treatment. Various drugs, such as quinine, diphenylhydantoin, procainamide, carbamazepine, asprin, and sulphinpyrazone, are being tried empirically with no definite benefit being shown from controlled clinical trials. The fact that diabetic subjects with only moderate alcohol intake had far fewer symptoms of peripheral neuropathy lends support to the view that moderation should be advised to diabetic individuals as a preventive measure in the development of peripheral neuropathy. It may simply be that asking a diabetic person who drinks alcohol excessively to moderate intake could prevent neuropathic symptoms from arising and hopefully may improve or reverse them when present.

ACKNOWLEDGMENTS: The authors wish to thank Sarah Dickson of the Diabetic Department, Royal Infirmary, Edinburgh, and Wilma Hepburn of the Medical Computing and Statistics Unit of Edinburgh University for their help in the data processing.

From the Diabetic and Dietetic Department, Royal Infirmary, Edinburgh, and the Medical Computing and Statistics Unit, Edinburgh University, Scotland.

Address reprint requests to David K. McCulloch, Diabetic and Dietetic Department, Royal Infirmary, Edinburgh, Scotland.

REFERENCES

[1] Krall, L. P., and Joslin, A. P.: General plan of treatment and diet regulation. *In* Joslin's Diabetes Mellitus. Philadelphia, Lea & Febiger, 1971, pp. 255–86.

[2] Malins, J. M.: *In* Clinical Diabetes Mellitus. London, Eyre and Spottiswoode, 1968, pp. 343–60.

[3] McCulloch, D. K., Campbell, I. W., Wu., F. C., Prescott, R. J., and Clarke, B. F.: The prevalence of diabetic impotence. Diabetologia. In press.

[4] Argov, Z., and Masoglia, F. L.: Drug-induced peripheral neuropathies. Br. Med. J. *1*: 663–66, 1979.

[5] Woolf, B.: On estimating the relation between blood groups and disease. Ann. Hum. Genet. *19*: 251–53, 1955.

[6] Cox, D. R.: *In* Analysis of Binary Data. London, Methuen, 1970, pp. 58–61.

[7] Cox, D. R.: *In* Analysis of Binary Data. London, Methuen, 1970, pp. 61–66.

[8] Walsh, J. C., and McLeod, J. G.: Alcoholic neuropathy, an electrophysiological and pathological study. J. Neurol. Sci. *10*: 457–69, 1979.

[9] Thomas, P. K., and Lascalles, R. G.: The pathology of diabetic neuropathy. Q. J. Med. *35*: 489–509, 1966.

rit. J. Psychiat. (1982), 140, 447–452

The Clinical Features of Diabetic Impotence: A Preliminary Study

C. G. FAIRBURN, F. C. W. WU, D. K. McCULLOCH, D. Q. BORSEY, D. J. EWING, B. F. CLARKE and J. H. J. BANCROFT

Summary: Twenty-seven diabetic men with erectile impotence were given physical and psychosexual assessments. Physical assessment included vascular and neurological evaluation. Psychosexual assessment was by means of a semi-structured interview. Seven potent diabetic men formed a control group. Patients with erectile failure had a varied clinical picture which differed from the stereotype of diabetic impotence: morning erections were preserved in over a half (55 per cent), eight patients (30 per cent) had intact spontaneous erections, and sexual interest was reduced in 12 patients (44 per cent). In 13 patients (48 per cent) ejaculation was disturbed and a further four patients (15 per cent) described unusual disorders of sexual function.

Within the group there were no differences in clinical picture between those with and without autonomic neuropathy, retinopathy or potential psychogenic factors.

There are probably half a million known diabetics n the United Kingdom and an equal or greater umber of people with symptomless, undetected iabetes (Jarrett and Keen, 1976). Surveys of diabetic ien using a variety of selection techniques indicate iat between 35 and 60 per cent have erectile impotence (Rubin and Babbott, 1958; Ellenberg, 1971; AcCulloch *et al*, 1980). Although these studies have icked control groups there is little doubt that this revalence is significantly greater than that found mong non-diabetic men in the general population Frank *et al*, 1978; Gebhard and Johnson, 1979).

Two forms of diabetes-related impotence are recogized. In the first, failure of erection occurs in the ontext of poor diabetic control. Erectile failure and oss of sexual interest accompany the general malaise, nd these symptoms reverse once the patient's physical ondition improves. This type of impotence is nonpecific and is found in other debilitating conditions Kolodny *et al*, 1979). The second form of impotence s said to be characteristic of diabetes. It is thought to e the result of a physical process and it is generally escribed as progressive and irreversible. All erections re affected, including those obtained spontaneously nd on waking, and it is associated with no loss of exual interest. 'Psychogenic' impotence, in contrast, s characterized by erectile failure confined to certain ircumstances (usually when with the sexual partner), ometimes complicated by a loss of sexual interest Cooper, 1972; Kolodny *et al*, 1974; Kockott *et al*, 980). The difference between the two clinical pictures is widely used in the assessment of erectile failure in diabetic men.

The validity of these clinical stereotypes has recently been questioned (Fairburn, 1981) and it has been suggested that many diabetic patients show 'intermediate' clinical features (Schiavi and Hogan, 1979). Furthermore, there have been reports of the successful use of sex therapy in the treatment of diabetic impotence, a supposedly irreversible condition (Renshaw, 1975, 1979).

The aim of this study was to provide a comprehensive description of the sexual function of a group of diabetic men with erectile failure and to relate this to physical and psychological factors likely to be relevant to the aetiology of their erectile disturbance.

Method

Subjects

Seventy-three diabetic men aged less than 55 years, attending the diabetic out-patient department at the Royal Infirmary, Edinburgh, were invited to join the study. Each had described partial or complete erectile failure of at least six months duration. Most subjects had been identified in a prevalence study three years earlier (McCulloch *et al*, 1980). Seven potent diabetic men were selected from the same population for comparison.

Thirty-four impotent subjects (47 per cent) did not wish to take part in the study. Of the remaining 39 patients, 27 completed each aspect of the study. The

mean age of the impotent group was 43.7 years (range 25–53 years; SD 8.0) and the mean duration of diabetes was 13.1 years (range 1–33 years; SD 7.3). The corresponding figures for the comparison group were 41.0 years (range 24–51 years; SD 9.3) and 12.4 years (range 3–27 years; SD 9.2).

Investigations

(i) A full medical history and physical examination were carried out.

(ii) Autonomic nerve function tests comprised five simple tests of cardiovascular reflex function. These were the Valsalva manoeuvre, lying-to-standing heart rate response, a measure of R-R interval variation (all assessing cardiac parasympathetic function), and the blood pressure responses to sustained handgrip and posture (assessing more widespread sympathetic abnormalities). These tests have been described in detail elsewhere (Ewing, 1978; Clarke *et al*, 1979; Ewing *et al*, 1980).

(iii) Psychosexual assessment was conducted by a psychiatrist experienced in the clinical management of sexual problems (C.G.F.). A semi-structured interview was designed for the purpose. For each item a standard initial probe question was used and followed by further questioning sufficient to clarify the answer. Replies were noted verbatim and coded during the interview. The major areas examined were as follows: the onset of sexual problem, present sexual function, present life circumstances, past sexual function and the effects of the sexual problem on the patient and his partner.

Each investigation was performed independently by different observers.

Statistical analysis

Where statistical comparisons were possible the Fisher exact probability test was used.

Results

Onset of sexual problem

The impotent patients gave a history of sexual difficulties lasting on average 4.4 years (range 1–8 years; SD 1.9) with a mean age at onset of 39.3 years (range 20–52 years; SD 8.0). Twenty-three of the 27 patients had diabetes when their sexual difficulties began, and two more were diagnosed as having diabetes within the next six months.

The clinical picture at onset varied. In 24 subjects the first symptom was a decline in either the strength or the duration of erection. Seventeen reported that both declined simultaneously; the remainder said they obtained an erection of normal strength, but it failed to last. Three patients described different modes of onset. One developed premature ejaculation for the first time when aged 44 years. This was in the cont of a good marriage and stable social circumstanc Four years later erectile failure supervened after period of increased anxiety over sexual performan A second patient aged 42 years complained of sem 'trickling out' of his erect penis during foreplay. Tl was a novel experience which was unaccompanied the sensation of orgasm and occurred before t patient was significantly aroused. Orgasm occurr later, but in the absence of ejaculation. Erectile failu developed after two months. The same pattern disturbance was present on masturbation. A thi patient aged 31 years complained of an increase in tl ease with which he obtained an erection. He began have numerous erections through the day, usually the absence of sexual thoughts. These erections caus him embarrassment, particularly as he sometim ejaculated. Twelve months later he ceased to ejacula with force; instead semen 'dribbled out' of his penis orgasm. Soon afterwards erectile failure developed.

By the end of the first six months, 26 of the 2 patients had experienced a degree of erectile failu and four had ceased to ejaculate despite continuing t achieve orgasm. One patient had developed an abno mality in the shape of his erect penis with it bendin upwards mid-way along the shaft so that it resembled smoker's pipe in profile. A second patient developed similar abnormality three years after the onset c erectile dysfunction.

Interest in sex remained intact throughout thi initial six months period in 23 of the 27 patients. Tw patients (ages 25 and 26 years) had a reduced interes in sex at the time of onset and in both these subject concurrent marital difficulties were prominent; in th two others (ages 38 and 52 years) interest in sex de clined sharply once erectile failure developed. Bot these patients had a history of premature ejaculatior and each described a resurgence of anxiety over sexua performance.

Present sexual function

Table I summarises the symptomatology of th impotent and non-impotent groups at the time o interview. The clinical picture was varied. The classical features of diabetic impotence, absent or reduced morning erections and intact sexual interest, were not present in a substantial proportion. Over half the impotent men obtained full erections on waking and a similar number had a reduced interest in sex. Most subjects described fluctuations in their degree of sexual interest.

Abnormalities of ejaculation were present in 13 of the impotent patients. In nine subjects there was a loss of the 'pumping sensation' associated with ejaculation. Those patients who masturbated said that semen

TABLE I

Sexual symptomatology in the impotent and control groups

xual symptomatology	Impotent group (N = 27)	(%)	Control group (N = 7)	(%)	Significance (Fisher test)
rectile failure	26*	(96)	0	(0)	—
npaired morning erections	12	(44)	1	(14)	NS
npaired spontaneous erections	19	(70)	0	(0)	P < 0.05
jaculatory disturbance	13	(48)	0	(0)	P < 0.05
educed interest in sex	12	(44)	0	(0)	P < 0.05

One patient in the impotent group did not have erectile impotence at the time of assessment. He had experienced intermittent erectile failure in the past.

owed out' of their penis at orgasm. Four patients ased to ejaculate at all, despite experiencing gasm. Only one of these patients described cloudy st-orgasmic urine suggestive of retrograde ejaculation. A change in the nature of the ejaculate was ted by three patients with a decrease in its volume d tendency to clot.

The degree of erectile failure was profound: only ur patients had a sufficiently firm erection to permit ginal penetration and intercourse. Despite this, ost patients insisted that they became sexually oused under appropriate circumstances. Eight of the potent patients were able to obtain erections on asturbating or spontaneously, and these tended to be mer than those obtained with their partner.

st sexual function

None of the seven potent diabetic men had a story of sexual dysfunction, whereas five of the potent patients had previously sought help for xual problems (Fisher exact probability test NS). wo of these patients had longstanding premature aculation, one had a history of delayed ejaculation d the remaining two had experienced an earlier isode of erectile failure. None of the patients desibed having erectile failure at times of poor diabetic ntrol.

iabetic complications and sexual symptomatology

(i) *Retinopathy:* When the impotent patients were bdivided into those with (N = 16) and without (N =) background, exudative or proliferative retinopathy e to their diabetes, no differences were found in the xual symptomatology of the two groups (Fisher act probability test NS).

(ii) *Autonomic neuropathy:* On the basis of cardiovascular autonomic function tests, the patients were divided into those with normal tests and those with one or more abnormal results. The sexual symptomatology of the two groups was similar (Fisher exact probability test NS). No difference emerged when the patients were further subdivided into those with cardiac parasympathetic abnormalities alone (N = 6) and those with more widespread additional sympathetic abnormalities (N = 5).

Psychological factors and sexual symptomatology

Two factors which might provide a psychological component to the erectile failure were the presence of previous sexual difficulties suggesting a vulnerability to sexual dysfunction and the existence of active marital dysharmony. One or both these factors was present in nine of the impotent patients, whereas they were absent from the potent group. (Fisher exact probability test NS). There were no significant differences in sexual symptomatology between those impotent patients with and without psychological problems (Fisher exact probability test NS).

Other factors liable to affect sexual function

Although the impotent patients were diagnosed as having diabetic impotence, many other factors were detected which might have been responsible for their sexual difficulties. At the time of onset, six were drinking heavily and two were still doing so at assessment (average consumption of at least 120 g of ethanol daily). In two patients, erectile failure and angina developed simultaneously following myocardial infarction. Seven patients had severely impaired exercise tolerance sufficient to make it difficult for them to climb two flights of stairs. One patient had undergone a lumbar sympathectomy for intractable

claudication. He described progressive erectile failure and an inability to ejaculate; however, his sexual interest and ability to become aroused and achieve orgasm were unimpaired. Two other patients were suspected of having multiple sclerosis. One patient had experienced intermittent dysarthria and ataxia. His sexual problems predated these symptoms by five years. The second patient had retrobulbar neuritis and a progressive weakness of both legs. He described erectile failure which had started three years earlier and this was accompanied by absent ejaculation, but intact orgasm. Three patients were taking drugs at the onset of their sexual problem which are known to interfere with sexual function (imipramine, amitriptyline and methyldopa) and at assessment one was taking chlorpromazine. Of the seven control patients, one had impaired exercise tolerance and another was taking imipramine.

Reactions to the sexual problem

The reaction of the patient and his partner to the onset of sexual difficulties was ascertained. Certain patterns of response were discernible (see Fig). The most common reaction (10 patients) was of increasing anxiety over the decline of sexual performance leading to a degree of sexual avoidance and reduced interest in sex (pathway A). Four patients accepted the problem: their attitude was that they should make the most of their sexual capabilities. This attitude developed gradually once the patient appreciated that such difficulties were common among diabetics and could be attributed to the disease: it was usually preceded by a period of anxiety and loss of sexual interest (pathway B). Two patients with a good knowledge of diabetes and its complications had this attitude from the outset (pathway C). In contrast, five patients accepted the problem passively, stating that they were unconcerned about the change in sexual function (pathway D). While a degree of denial might have been present, all five indicated that sex had never been of great importance to them. Two of these patients had experienced erectile failure in the past.

In ten instances the patient's partner reacted adversely to the sexual difficulty. Six of the wives blamed themselves for the problem thinking that they were no longer attractive to their partners, whereas in four cases the reaction was of anger and resentment. Both of these responses led to the avoidance of sex. Knowledge that the sexual problem might be secondary to the diabetes appeared to help resolve the self-blame, but it did little to neutralize the other, more hostile response.

Discussion

Unlike previous studies of diabetic impotence a small number of patients have been examined in detail, the number being limited by the intensive and personal nature of the investigations. Most other studies have examined large numbers of patients from an epidemiological standpoint. The two approaches complement one another.

The patient sample may have been biased, as almost half of those invited did not wish to participate in the study. However, this is unlikely to have affected the principal conclusion that the clinical picture of diabetic impotence is more varied than previously suggested. Marked differences were found between individuals and within individuals over time, and certain symptoms such as disturbed ejaculation were more common than hitherto described.

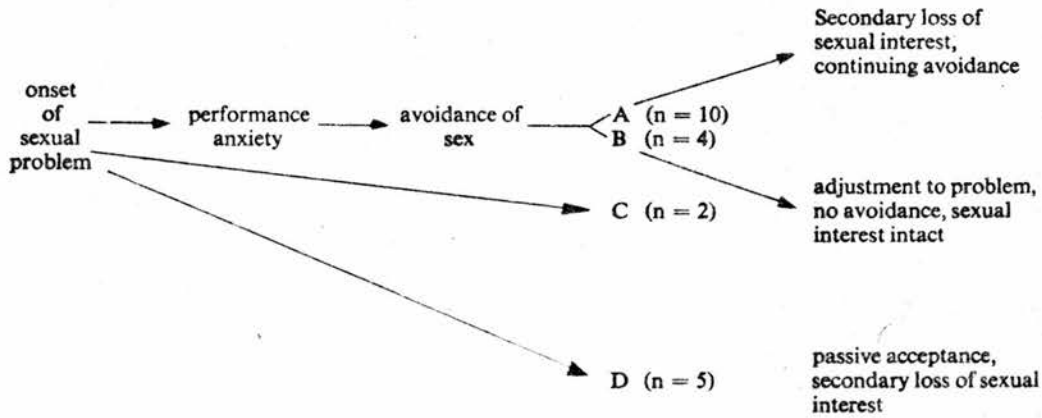


FIG.—Reactions to the sexual problem.
* n = number of patients who clearly showed a particular reaction.

Erectile failure was not necessarily the first symptom of sexual dysfunction. One patient's problem started with late onset premature ejaculation, another complained of an inconvenient increase in the ease with which he obtained an erection, and a third noticed a change in his ability to ejaculate. At the onset the severity of sexual dysfunction varied from day to day, but this variability declined with time.

Failure to obtain morning and spontaneous erections is said to be characteristic of diabetic impotence (Cooper, 1972; Kolodny *et al*, 1974). However, in this study full morning erections were experienced by over half the impotent patients and spontaneous erections by almost a third. These results are different from those predicted, but are not altogether at variance with other reports: almost a half of the patients studied by Rubin and Babbott (1958) and Scott *et al* (1980) had intact morning erections. The alteration in the shape of erection reported by two patients cannot be explained. There was no history of penile trauma or evidence of Peyronie's disease on palpation.

Ejaculatory disturbance was present in almost half the patients. The form of disturbance varied. Retrograde ejaculation as judged by the presence of cloudy post-orgasmic urine was described by only one patient. Three others had absent ejaculation, but unremarkable post-orgasmic urine. In these subjects the production of ejaculate may have ceased; alternatively, emission may have been impaired. The most common ejaculatory disorder, present in over a third of the sample, was the absence of the pumping sensation that normally accompanies ejaculation: 10 patients described semen seeping out of their erect or flaccid penis at, or before orgasm. This phenomenon did not resemble the emission experienced by patients with severe premature ejaculation since it often occurred prior to orgasm. It is also unlikely to have been due to profuse secretion from the periurethral glands since all the patients described it as a novel phenomenon. Instead it is probable that this abnormality arose from a subtle disruption of the ejaculatory process.

Sexual interest is considered to remain intact in diabetic impotence (Cooper, 1972; Kolodny *et al*, 1974). In this sample, the majority of the sexual difficulties developed in the context of intact interest in sex, but in almost half the patients this subsequently declined. It appeared that sexual interest was variably affected and any decrease was not necessarily irreversible. When sexual interest did decline, it seemed that this represented a psychological response to the sexual failure.

Although no associations were found between retinopathy or autonomic neuropathy and the form of sexual dysfunction, the numbers of patients in this study are too small to permit firm conclusions. There was also no clear association between the presence of psychological factors and the pattern of sexual dysfunction, although where such factors were present, patients were more likely to have intact morning and spontaneous erections and a reduced interest in sex. These features are precisely those one would predict on clinical grounds.

Since it is likely that the various aetiological factors interact, it is not surprising that no simple associations emerged. It is probable that the erectile failure of many diabetic men is in part the result of a progressive physical disorder such as autonomic neuropathy. Superimposed upon this is the psychological reaction of the patient and his partner which may significantly worsen the problem. On the basis of the present findings it seems that this reaction may take various forms. It is likely to depend on the couple's and each individual's prior experience of sexual dysfunction, as well as their personalities, their awareness of impotence as a complication of diabetes, their evaluation of the importance of sex and potency, and the quality of their relationship.

The concept of diabetic impotence is misleadingly oversimplified. It is preferable to view diabetic men as especially prone to physical factors liable to disturb sexual function. These will interact with psychological factors to produce a variety of clinical pictures. If diabetic impotence is viewed in this way it may be possible to improve the gloomy prognosis by using appropriate counselling to minimize the psychological reaction to sexual dysfunction.

References

CLARKE, B. F., EWING, D. J. & CAMPBELL, I. W. (1979) Diabetic autonomic neuropathy. *Diabetologia*, **17**, 195–212.

COOPER, A. J. (1972) Diagnosis and management of 'endocrine impotence'. *British Medical Journal*, *ii*, 34–6.

ELLENBERG, M. (1971) Impotence in diabetes: the neurologic factor. *Annals of Internal Medicine*, **75**, 213–19.

EWING, D. J. (1978) Cardiovascular reflexes and autonomic neuropathy. *Clinical Science and Molecular Medicine*, **55**, 321–7.

—— CAMPBELL, I. W. & CLARKE, B. F. (1980) Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Annals of Internal Medicine*, **92**, 308–11.

FAIRBURN, C. G. (1981) The sexual problems of diabetic men. *British Journal of Hospital Medicine*, **25**, 484–91.

FRANK, E., ANDERSON, C. & RUBINSTEIN, D. (1978) Frequency of sexual dysfunction in 'normal' couples. *New England Journal of Medicine*, **299**, 111–15.

GEBHARD, P. H. & JOHNSON, A. B. (1979) *Marginal Tabulations of the 1938–1963 Interviews Conducted by the Institute for Sex Research*. Philadelphia: W. B. Saunders.

JARRETT, R. J. & KEEN, H. (1976) Hyperglycaemia and diabetes mellitus. *Lancet*, *ii*, 1009–12.

KOCKOTT, G., FEIL, W., REVENSTORF, D., ALDENHOFF, J. & BESINGER, U. (1980) Symptomatology and psychological aspects of male sexual inadequacy: results of an experimental study. *Archives of Sexual Behaviour*, **9**, 457–75.

KOLODNY, R. C., KAHN, C. B., GOLDSTEIN, H. H. & BARNETT, D. M. (1974) Sexual dysfunction in diabetic men. *Diabetes*, **23**, 306–9.

—— MASTERS, W. H. & JOHNSON, V. E. (1979) *Textbook of Sexual Medicine*. Boston: Little, Brown.

MCCULLOCH, D. K., CAMPBELL, I. W., WU, F. C., PRESCOTT, R. J. & CLARKE, B. F. (1980) The prevalence of diabetic impotence. *Diabetologia*, **18**, 279–83.

RENSHAW, D. C. (1975) Impotence in diabetics. *Diseases of the Nervous System*, **36**, 369–71.

—— (1979) Diabetic impotence—inevitable or imposed? *British Journal of Sexual Medicine*, **6**, 48–51.

RUBIN, A. & BABBOTT, D. (1958) Impotence and diabetes mellitus. *Journal of the American Medical Association*, **168**, 498–500.

SCHIAVI, R. C. & HOGAN, B. (1979) Sexual problems in diabetes mellitus: psychological aspects. *Diabetes Care*, **2**, 9–17.

SCOTT, F. B., FISHMAN, I. J. & LIGHT, J. K. (1980) An inflatable penile prosthesis for treatment of diabetic impotence. *Annals of Internal Medicine*, **92**, 340–2.

*Christopher G. Fairburn, M.A., M.Phil., M.R.C.Psych., *Lecturer in Psychiatry, University Department of Psychiatry, Royal Edinburgh Hospital, Edinburgh*

F. C. W. Wu, B.Sc., M.R.C.P., *Senior Registrar, Diabetic Department, Royal Infirmary, Edinburgh*

David K. McCulloch, B.Sc., M.R.C.P., *Medical Registrar, Diabetic Department, Royal Infirmary, Edinburgh*

David Q. Borsey, M.B., M.R.C.P., *Medical Registrar, Royal Infirmary, Edinburgh*

David J. Ewing, M.D., M.R.C.P., *Welcome Trust Senior Lecturer in Medicine, University of Edinburgh*

Basil F. Clarke, F.R.C.P., *Consultant Physician, Diabetic Department, Royal Infirmary, Edinburgh*

John H. J. Bancroft, M.D., M.R.C.P., F.R.C.Psych., *Clinical Consultant, Medical Research Council Reproductive Biology Unit, Edinburgh*

* Present post: *Research Psychiatrist, University Department of Psychiatry, Warneford Hospital, Oxford.*

(*Received 11 May; revised 26 November 1981*)

PAPERS AND SHORT REPORTS

Alcohol: another risk factor for diabetic retinopathy?

R J YOUNG, D K McCULLOCH, R J PRESCOTT, B F CLARKE

Abstract

In a five year prospective study clinical features associated with the development and progress of retinopathy were sought in 296 randomly selected diabetic men aged 20-59. None had ophthalmoscopically detectable retinopathy initially, but during follow up 66 developed the condition (47 background, 10 exudative, 9 proliferative). Linear logistic analyses (two tailed tests) showed that the initial features independently predictive of retinopathy were duration of diabetes, poor glycaemic control, impotence, and—unexpectedly—heavy alcohol consumption. Poor glycaemic control in the interim and proteinuria at review were also associated with the development of retinopathy. No relation was found with smoking or obesity. Glycaemic control and alcohol consumption were therefore the only aetiologically relevant associations identified. The development of severe retinopathy (exudative and proliferative) showed a particular association with heavy alcohol consumption, occurring in nine of the 70 heavy drinkers (13%) compared with 10 (4·4%) of the rest.

Alcohol consumption may be an important independent factor associated predictively with sight threatening diabetic retinopathy.

Introduction

Diabetic retinopathy remains a major cause of blindness. Various factors have been suggested as associated with retinopathy in cross sectional studies. A relation between duration of diabetes and the development of retinopathy has long been recognised,[1] and mean clinic blood glucose concentrations are reported to be higher, particularly in severe retinopathy.[2 3] Published data related to other factors such as cigarette smoking,[4-7] obesity,[2 8-11] blood pressure,[8-18] and genetic susceptibility[19-21] have produced conflicting conclusions well summarised by Dornan *et al.*[8]

Only two studies have examined prospectively clinical features predictive of retinopathy. Pirart confirmed the effect of duration of diabetes and substantiated the importance of glycaemic control, but a vast drop out rate limited the value of his study.[2] In Pima Indians, who have a high prevalence of type II (non-insulin-dependent) diabetes, severity of disease, a raised plasma glucose concentration, proteinuria, neuropathy, and systolic blood pressure all had some predictive value.[18]

Much therefore remains uncertain about the factors responsible for the remarkable differences commonly observed between individual diabetics with respect to both the presence and severity of retinopathy. A prospective study of diabetic impotence in a large number of diabetic men[22] allowed us also to consider clinical features which might be predictive of diabetic retinopathy.

Patients and methods

At the outset 541 men aged 20-59 years were studied; 101 had been selected at random from the total male clinic population of the same age range and it was shown that the study group was fully representative of the male diabetic clinic population.[22] During the period of follow up 36 patients left the area and a further 22 became untraceable. In addition, six patients refused reinterview and 11 were unsuitable (five severe psychiatric illness, three severe cerebrovascular disease, one traumatic brain damage, two not diabetic). Of the remaining 466 men, 63 had died leaving 403 who were re-examined. The mean interval between the first and second study examinations was 4 years 8 months (range 3 years 8 months to 6 years 2 months). The same detailed questionnaire was completed at the initial and follow up visits. Age, body weight, duration of diabetes, form of treatment, other drug treatment, smoking (cigarettes a day), and alcohol intake (measures a week) were recorded. In the analysis alcohol intake was divided simply into none to moderate ($\leq$10 pints (5·7 l) of beer or equivalent a week) and heavy ($>$10 pints of beer or equivalent a week). Direct inquiry elicited past medical history, symptoms of ischaemic heart disease, peripheral vascular disease, sexual function, and diabetic peripheral and autonomic neuropathy. Initially the six most recent clinic blood glucose values were averaged as an index of

Diabetic Department, Royal Infirmary, Edinburgh, and Department of Medical Statistics, University of Edinburgh
R J YOUNG, MRCP, senior registrar
D K McCULLOCH, MRCP, registrar
R J PRESCOTT, PHD, senior lecturer
B F CLARKE, FRCPED, consultant physician

Correspondence to: Dr R J Young, Diabetic Department, Royal Infirmary, Edinburgh EH3 9YW.

glycaemic control, and at review all of the values obtained during the intervening period were averaged. Retinopathy was assessed by direct ophthalmoscopy of both fundi through dilated pupils in a dark cubicle; findings were recorded as normal (grade 1), microaneurysms with or without dot haemorrhages (grade 2), soft or hard exudates (grade 3), and neovascularisation (grade 4). Proteinuria (Albustix) was recorded as 0, ±, +, ++, or +++.

Statistical analysis was principally by the application of linear logistic models.[23] For binary responses (for example, retinopathy/no retinopathy) these models are the equivalent of the more familiar multiple regression models,[24] which can be used only for continuous response variables (for example, weight). Thus the linear logistic model allows the simultaneous assessment of the possible influence of several interrelated variables on the development of retinopathy. Two tailed likelihood ratio tests were employed to determine the significance of individual terms. The analysis had two stages. In the first stage only variables relating to the initial examination were included in the model. In the second stage the significant variables from the first stage were retained in the model and the additional effect of variables relating to the follow up period were assessed.

TABLE I—*Progression of retinopathy over 5 years (mean 4 years 8 months; range 3 years 8 months to 6 years 2 months) in 403 diabetic men*

Initial grade*	No of patients	Grade* at review			
		1	2	3	4
1	296	230	47	10	9
2	66	16	31	6	13
3	23		3	7	13
4	18				18
Total	403	246	81	23	53

*1 = No retinopathy. 2 = Microaneurysms ± haemorrhages. 3 = Exudates. 4 = Neovascularisation.

Results

Table I shows the fundoscopic findings initially and at review in the 403 men who were followed up. Initially no retinopathy was seen in 296, of whom 66 subsequently developed retinal changes. Table II lists the features significantly associated with the development of retinopathy in this group. From the logistic model the estimated relative risk of developing retinopathy of any grade in "heavy" compared with "none to moderate" drinkers was 2·25 with 95% confidence limits of 1·15 to 4·42. Table II also suggests that heavy drinkers were more likely to develop severe retinopathy. This was confirmed when the data were analysed to extract features associated with progression of retinopathy from grade 1 to grade 3 or 4 during the review period. The only significant features then were original alcohol intake ($p = 0·02$), original impotence ($p = 0·03$), and proteinuria at review ($p < 0·001$). The estimated relative risk for heavy drinkers of developing severe retinopathy was 3·5 but the 95% confidence limits were wide (1·2 to 8·4) owing to small numbers.

No other features appeared in the fitted logistic model and, in particular, the other potentially causal factors—smoking and body mass index—did not show any evidence of association with retinopathy even when considered separately.

TABLE II—*Development of retinopathy over 5 years (mean 4 years 8 months; range 3 years 8 months to 6 years 2 months) in 296 diabetic men originally free of retinopathy; significantly associated features. (Percentages given in parentheses)*

		Grade of retinopathy at review				Total: all groups	Significance*
		1	2	3	4		
Initial features							
Duration of diabetes (years)	≤4	137 (91)	9 (6)	2 (1)	3 (2)	151	$p < 0·0001$
	5-9	59 (71)	14 (17)	5 (6)	5 (6)	83	
	≥10	34 (55)	24 (39)	3 (5)	1 (2)	62	
Glycaemic control (mmol/l)†	<9	107 (87)	12 (10)	3 (3)	0	116	$p = 0·02$
	9-14	88 (73)	21 (17)	6 (5)	6 (5)	121	
	>14	41 (69)	14 (24)	1 (2)	3 (5)	59	
Sexual function	Potent	185 (83)	28 (13)	7 (3)	3 (1)	223	$p < 0·001$
	Impotent	45 (62)	19 (26)	3 (4)	6 (8)	73	
Alcohol intake (measures/week)	≤10	181 (80)	35 (15)	5 (2)	5 (2)	226	$p = 0·02$
	>10	49 (70)	12 (17)	5 (7)	4 (6)	70	
Features at review							
Glycaemic control (mmol/l)†	<9	61 (87)	5 (7)	3 (4)	1 (1)	70	$p < 0·001$
	9-14	127 (80)	21 (13)	5 (3)	5 (3)	158	
	>14	25 (57)	14 (32)	2 (5)	3 (7)	44	
Proteinuria	Nil or intermittent	224 (81)	41 (15)	6 (2)	5 (2)	276	$p < 0·001$
	Persistent	6 (30)	6 (30)	4 (20)	4 (20)	20	

*Based on likelihood ratio tests from linear logistic model.
†Values are means of clinic blood glucose concentrations as detailed in text; 24 records missing at review.
Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

Discussion

The prevalence of diabetic retinopathy is about 80% after 25 years of diabetes in otherwise unselected diabetics, but only a small proportion (roughly 15%) will have developed proliferative retinopathy or maculopathy.[25] In clinical practice it is noticeable that in apparently similar patients retinopathy develops to greatly varying degrees. Thus, although sight threatening retinopathy will usually not develop unless there is hyperglycaemia of substantial duration, glycaemic control and duration of diabetes often seem insufficient in themselves to account for the variations observed. Numerous studies have therefore sought aetiopathogenic factors other than glycaemic control, including genetic susceptibility, body mass index, blood pressure, and smoking, for all of which the evidence is conflicting. We have investigated the influence of some of these factors and additionally, for the first time, the effect of alcohol.

Before discussing the results further it is important to consider the following. Unlike cross sectional studies, prospective studies such as ours may identify predictive as well as coexistent features with respect to a dependent variable such as retinopathy. They cannot, however, determine whether such associations are causal. Nevertheless, based on what we know about the disease the statistically significant and non-significant features in the analysis may be divided into those such as glycaemic control and alcohol consumption which might have an aetiological role in retinopathy and those such as impotence and proteinuria which are probably just other manifestations of generalised microangiopathy. It is the former with which this study was concerned particularly, and the statistical analysis ensured that inclusion of the latter in the model did not obscure or create any significant associations with the former. Finally, almost all prospective studies have the inevitable shortcoming that follow up is incomplete. In our series 14% of the original cohort were "lost" and 12% died. We have no evidence that those who moved away or became untraceable differed ap-

preciably from the group reviewed. With respect to death it might be argued that risk factors for retinopathy may be obscured if they also increase the risk of early death. Features at the outset significantly associated with death during the review period were proteinuria, previous myocardial infarction, symptomatic autonomic neuropathy, and retinopathy.[22] There was therefore an underrepresentation of initially retinopathy free men among those who died, but none of the features predictive of death are probable aetiological factors for retinopathy, and so it is unlikely that this would influence the results.

Apart from duration of diabetes our prospective study in men initially clinically free of retinopathy showed significant relations between the development of retinopathy of any grade and two features of potential aetiological relevance—glycaemic control and alcohol intake. Body mass index and smoking were included in the analysis but no relation was found; this agrees with other studies.[2 4 7 10 21] We did not look for a genetic influence or an association with blood pressure.

The importance of the degree of glycaemic control in the development and progression of diabetic retinopathy remains controversial. There are very few prospective data from which the role of glycaemic control in the development of retinopathy may be deduced, but both Pirart's study and the six year prospective study of Pima Indians found positive associations.[2 10] Retrospective studies have found a relation between the mean of many clinic blood glucose estimations and the degree of resulting retinopathy.[3 21] On the other hand, in intervention studies data relating the degree of glycaemic control to the progression of established retinopathy have produced contradictory results.[26 27] Our prospective data on clinical retinopathy arising as a new complication support the contention that glycaemic control is an important determinant of the development of retinopathy despite the poor index of glycaemic control used. Thus both initially and during follow up there were significant associations of the degrees of glycaemic control with the development of retinopathy of any grade. Inspection of the data also suggests that severe retinopathy was more likely to develop if glycaemic control was poor during follow up. This was not, however, statistically significant.

The surprising finding was the relation between alcohol intake initially and the subsequent development of retinopathy. So far as we know no such relation has been reported. It is clearly a relatively small effect, but none the less significant, and the particular association with the more severe degrees of retinopathy is noteworthy. If this were a causal relation it might account, in a few diabetics, for otherwise inexplicably rapid progression to sight threatening retinopathy. If we speculate further, potential causal mechanisms might operate via synergistic glucose and alcohol mediated metabolic tissue damage or through the intermediary of hypertension. Alternatively, high alcohol intake might just be a marker for some other habit—possibly poor diet—which is the true causal association.

Whatever the explanation we have shown prospectively the association of two potentially aetiologically explanatory variables—glycaemic control and alcohol intake—with both the development and the progress of diabetic retinopathy. Further primary intervention studies are required to determine the precise degrees of influence and mechanisms of action of these factors.

References

1 Caird FI, Pirie A, Ramsell TG. *Diabetes and the eye*. Oxford: Blackwell, 1969:30-1,72-7,85,88-91.

2 Pirart J. Diabetes mellitus and its degenerative complications. A prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care* 1978;**1**:168-88.

3 Dornan T, Mann JI, Turner R. Factors protective against retinopathy in insulin-dependent diabetics free of retinopathy for 30 years. *Br Med J* 1982;**285**:1073-7.

4 Christiansen JS. Cigarette smoking and prevalence of microangiopathy in juvenile-onset insulin-dependent diabetes mellitus. *Diabetes Care* 1978;**1**:146-9.

5 Paetkau ME, Boyd TAS, Winship B, Grace M. Cigarette smoking and diabetic retinopathy. *Diabetes* 1977;**26**:46-9.

6 Neilsen MM, Hjollund E. Smoking and diabetic microangiopathy. *Lancet* 1978;ii:533-4.

7 West KM, Erdreich LS, Stoder JA. Absence of a relationship between smoking and diabetic microangiopathy. *Diabetes Care* 1980;**3**:250-2.

8 Job D, Eschwege E, Tchobroutsky G, Guyot-Argenton C, Aubry J-P, Derot M. Diabetic retinopathy, duration of diabetes and risk factors of atherosclerotic cardiovascular disease. *Acta Diabetol Lat* 1975;**12**:1-8.

9 Hunter PR, Heath H, Bloom A. A clinical comparison between diabetics with no retinopathy after 15 years and severe, deteriorating retinopathy. *Diabetologia* 1977;**13**:403.

10 Szabo AJ, Stewart AG, Joron GE. Factors associated with increased prevalence of diabetic retinopathy; a clinical survey. *Can Med Assoc J* 1967;**97**:286-92.

11 Nilsson SE, Nilsson JE, Frostberg N, Emilsson T. The Kristianstad survey. II. Studies in a representative adult diabetic population with special reference to comparison with an adequate control group. *Acta Med Scand* 1967;**469**,suppl:1-42.

12 Keen H. The prevalence of blindness in diabetics. *J R Coll Physicians Lond* 1972;**7**:50-60.

13 Adler R, Freedman J, Kuhar N, Gombos GM. Various parameters of diabetic retinopathy among clinic populations. *Ann Ophthalmol* 1975;**7**:1447-54.

14 West KM, Erdreich LJ, Stober JA. A detailed study of risk factors for retinopathy and nephropathy in diabetes. *Diabetes* 1980;**29**:501-8.

15 Kornerup T. Blood pressure and diabetic retinopathy. *Acta Ophthalmol (Copenh)* 1957;**35**:163-74.

16 Balcdimos MC, Aiello LM, Gleason RE, Marble A. Retinopathy in mild diabetes of long duration. *Arch Ophthalmol* 1969;**B1**:660-6.

17 Kohner EM, Fraser TR, Joplin GF, Oakley NW. The effect of diabetic control on diabetic retinopathy. In: Goldberg MF, Fine SL, eds. *Symposium on the treatment of diabetic retinopathy*. Washington, DC: US Government Printing Office, 1968:119-28. (PHS publication No 1890.)

18 Knowler WC, Bennett PH, Ballintine EJ. Increased incidence of retinopathy in diabetics with elevated blood pressure. *N Engl J Med* 1980;**302**:645-50.

19 Dornan TL, Ting A, McPherson CK, *et al*. Genetic susceptibility to the development of retinopathy in insulin-dependent diabetics. *Diabetes* 1982;**31**:226-31.

20 Pyke DA, Tattersall RB. Diabetic retinopathy in identical twins. *Diabetes* 1973;**22**:613-8.

21 Gray RS, Starkey IR, Rainbow S, *et al*. HLA antigens and other risk factors in the development of retinopathy in type 1 diabetes. *Br J Ophthalmol* 1982;**66**:280-5.

22 McCulloch DK, Young RJ, Prescott RJ, Campbell IW, Clarke BF. The natural history of impotence in diabetic men. *Diabetologia* (in press).

23 Cox DR. The linear logistic model. *Analysis of binary data*. London: Methuen, 1970:14-29.

24 Armitage P. Multiple regression and multivariate analysis. *Statistical methods in medical research*. Oxford: Blackwell, 1971:302-20.

25 Lestradet H, Papoz L, Hellouin de Menibus CL, *et al*. Long term study of mortality and vascular complications in juvenile-onset (type 1) diabetes. *Diabetes* 1981;**30**:175-9.

26 Job D, Eschwege E, Guyot-Argentor C, Aubrey JP, Tchoubroutsky G. Effect of multiple daily injections on the course of diabetic retinopathy. *Diabetes* 1976;**25**:463-9.

27 Lauritzen T, Frost-Larsen K, Larsen H-W, *et al*. Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin-dependent diabetics. *Lancet* 1983;i:200-4.

(*Accepted 31 January 1984*)

THE TEETH, AND THEIR MEDICINES—If you will keep your teeth from rotting, or aching, wash your mouth continually every morning with juice of Lemons, and afterwards rub your teeth either with a Sage-leaf, or else with a little Nutmeg in powder; also wash your mouth with a little fair water after meats; for the only way to keep teeth sound, and free from pain, is to keep them clean. *To keep Teeth white*—Dip a little piece of white cloth in Vinegar of Quinces, and rub your gums with it, for it is of a gallant binding quality, and not only makes the teeth white, but also strengthens the gums, fastens the teeth, and also causeth a sweet breath. *To fasten the Teeth*—Seethe the roots of Vervain in old Wine, and wash your teeth often with them, and it will fasten them. *For the Tooth-ache*—Take the inner rind of an Elder-tree, and bruise it, and put thereto a little Pepper, and make it into balls, and hold them between the teeth that ache. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)

BIBLIOGRAPHY

Abelson, D. (1975), Journal of Urology, 113, 636.

Andersen, J.T., Bradley, W.E. (1976), British Journal of Urology, 48, 341.

Anderson, B.J., Auslander, W.F. (1980), Diabetes Care, 3, 696.

Ando, S., Rubens, R., Poloss, T., Vermeulen, A. (1979), In Recent Progress in Andrology, New York Academic Press.

Ansari, J.M. (1975), British Journal of Psychiatry, 127, 337.

Armitage, P. (1971), In Statistical Methods in Medical Research, Oxford: Blackwell.

Bancroft, J.H. (1977), Psychological Medicine, 7, 553.

Bancroft, J.H., Wu, F.C.W. (1982), Archives of Sexual Behaviour.

Baker, H.W.G., Burger, H.G., de Kretser, D.M. et al (1976), Clinical Endocrinology, 5, 349.

Berike, A. (1979), Medical Aspects of Human Sexuality, 13, 117.

Bennet, F., Evans D.F. (1976), Journal of Physiology, 263, 105.

Bohlen, J. (1981), Urologic Clinics of North America, 8, 119.

Bors, E., Camarr, A.E. (1960), Urological Survey, 10, 191.

Bradley, W.E., Timm, G.W., Scott, F.B. (1975), Urology, 5, 424.

Bradley, W.E., Timm, G.W., Rockswold, G.L., Scott, F.B. (1975), Journal of Urology, 114, 891.

Bradley, W.E. (1976), Mayo Clinic Proceedings, 51, 329.

Bradley, W.E. (1977), Journal of Urology, 118, 412.

Bradley, W.E. (1980), Annals of Internal Medicine, 92 (Part 2), 323.

Bremer, J. (1959) Asexualisation: A follow-up Study of 244 Cases, New York: Macmillan.

Campbell, I.W., Ewing D.J., Clarke, B.F., Duncan, L.J.P. (1974), British Medical Journal, ii, 638.

Canning, J.R., Bowers, L.M., Lloyd, F.A., Cottrell, T.L.C. (1963), Surgical Forum, 14, 298.

Champeyroux, J., Moinade, S., Gaillard, D., Boucher, D. (1978), La Nouvelle Presse Medicale, 7, 1007.

Charreau, E.H., Calvo, J.C., Tesone, M., de Souzvalle, L.B., Barono, J.L., (1978), Journal of Biological Chemistry, 253, 2504.

Clarke, B.F., Ewing, D.J., Campbell, I.W. (1979), Diabetologia, 17, 195.

Comhaire, F. and Vermeulen, A. (1975), Journal of Clinical Endocrinology, 40, 824.

Conti, G. (1952), Acta Anatomica, 14, 217.

Cooper, A.J. (1970), British Medical Journal, i, 157.

Cooper, A.J. (1971), Psychosomatics, 12, 235.

Cooper, A.J. (1972), British Medical Journal, i, 34.

Cornu, F. (1973), Katamnesen bei Kastrierten Sittlichkeitsdelinquenten aus Forensisch - Psychiatrischer Sicht. Basel: S. Karger.

Cox, D.R. (1970), In Analysis of Binary Data, London, Methuen.

Daubesser, J-C., Meuenier, J-C., Wilmotte, J., Luyckx, A.S. (1978), Diabetes and Metabolism, 4, 233.

Davidson, J.M., Kwan, M., Greenleaf, W.J. (1982), Clinics in Endocrinology and Metabolism, 11, (3), 599.

Deckert, T., Simonsen, S.E., Poulsen, J.E. (1967). Diabetes, 16, 728.

Distiller, L.A., Sagel, J., Morley, J.E., Joffe, B.F., Seftel, H.C. (1975), Diabetes, 24, 378.

von Ebner, V. (1900), Verh. Anat. Ges., 14, 79.

Ellenberg, M. (1971). Annals of internal Medicine, 75, 213.

Ellenberg, M. (1980), Annals of Internal Medicine, 92, 331.

Engel, G., Burnham, S.J., Carter, M.F. (1978), Fertility and Sterility, 30, 687.

Ewing, D.J., Campbell, I.W., Burt, A.A., Clarke, B.F. (1973), Lancet, ii, 1354.

Ewing, D.J., Campbell, I.W., Clarke, B.F. (1976), Lancet, i, 601.

Ewing, D.J., Campbell, I.W., Murray, A., Neilson, J.M.M., Clarke, B.F. (1978), British Medical Journal, i, 145.

Ewing, D.J., Campbell, I.W., Clarke, B.F. (1980), Quarterly Journal of Medicine, 193, 95.

Ewing, D.J., Campbell, I.W., Clarke, B.F. (1980), Annals of Internal Medicine, 92(2), 308.

Ewing, D.J., Campbell, I.W., Clarke, B.F. (1981), Lancet, i, 183.

Faerman, I., Maler, M., Jadzinsky, M., Alvarez, E., Fox, D., Zilbervarg, J., Cibeira, J.B., Colinas, R. (1971), Diabetologia, 7, 168.

Faerman, I., Vilar, O., Rivarola, M.A., Rosner, J.M., Jadzinsky, M.N., Fox, D., Perez Loret, A., Bernstein-Hahn, L., Saraceni, D. (1972), Diabetes, 21, 23.

Fisher, C. (1966), Dreaming and Sexuality, in Psychoanalysis - A General Psychology: Essays in Honor of Heinz Hartman. Eds Loewenstein, R.M., Newman, L.M. and Schur, M., New York: International University Press, pp 537-563.

Fisher, C., Schiavi, R.C., Lear, H., et al (1975), Archives of General Psychiatry, 36, 431.

Fisher, C., Schiavi, R.C., Edwards, A., et al (1979), Archives of General Psychiatry, 36, 431.

Foglia, V.G., Rosner, J.M., Cattaneo, D.E., Perlata, A., Raymos, M., Lema, B.E. (1969), Hormone and Metabolic Research, 1, 72.

Fournier, A.M., Huguet, J.F. (1968), Journal de Radiologie, d'Electrologie et de Medicine Nucleaire, 49, 515.

Fox, C.A., Ismail, A., Love, D.N., Kirkham, K.E., Loraine, J.A. (1972), Journal of Endocrinology, 52, 51.

Franks, S., Jacobs, H.S., Martin, M., Nabarro, J.D.N. (1978), Clinical Endocrinology, 8, 277.

Froland, A., Hagen, C., Lauritzen, E. (1977) Lancet, i, 45.

Gaskell, P. (1971), Canadian Medical Association Journal, 105, 1047.

Gattucio, F., Porcelli, P., Morici, V., Lobartolo, G., Janni, A. (1979), In Recent Progress in Andrology, New York, Academic Press.

Geisthovel, W., Niedergerks, U., Morgner, K.D., Willms, B., Mitzkat, H.J. (1975), Medizinishe Klinik, 70, 1417.

Ginestie, J-F., Romieu, A. (1976), In Radiologic Exploration of Impotence, London, Martinus Nykoff Medical Division.

Gray, C.D., Smith, E.R., Dorsa, D.M., Davidson, J.M. (1981), Endocrinology, 109, 1597.

Harris, J.D., Jepson, R.P. (1965), Australian and New Zealand Journal of Surgery, 34, 211.

Harter, M., Balarac, N., Pourcher, P., Koslowski, J.M., Krebs, B., Ramaioli, A. (1976), Lancet, ii, 961.

Hauser, S.T. and Pollets, D. (1979) Diabetes Care, 2, 227.

Heim, N., Hursch, C.J. (1979), Archives of Sexual Behaviour, 8, 281.

Heim, N. (1981), Archives of Sexual Behaviour, 10, 11.

Herman, A., Adar, R., Rubinstein, Z. (1978), Diabetes, 27, 975.

Hosking, D.J., Bennet, T., Hampton, J.R., Evans, D.F., Clark, A.J., Robertson, G. (1979), British Medical Journal, ii, 1394.

Hunt, E.L., Bailey, D.W. (1961), Acta Endocrinologica, 38, 432.

Hunter, P.R., Anderson, J., Lunn, T.A., Horrobin, D.F., Boyns, A.R., Cole, E.N. (1974), Lancet, i, 1237.

Ismail, A., Davidson, D.W., Loraine, J.A., et al (1970). In Reproductive Endocrinology (Ed.) Irvine, W.J., pp 138-147. Edinburgh: Livingstone.

Jensen, S.B., Hagen, C., Froland, A., Petersen, P.B. (1979), Acta Medica Scandinavica (Supplementum) 624, 65.

Kaplan, H.S. (1974) The New Sex Therapy. New York: Brunner Mazel.

Karacan, I. (1961), Behaviour Research, Methods and Instrumentation, 1, 251.

Karacan, I., Goodenough, D.R., Shapiro, A., Starker, S. (1966) Archives of General Psychiatry, 15, 183.

Karacan, I., Williams, R.L., Thornby, J.I., Salis, P.J. (1975) American Journal of Psychiatry, 132, 932.

Karacan, I., Salis, P.J., Thornby, J.I., Williams, R.L. (1976) Waking and Sleeping, 1, 27.

Karacan, I., Scott, F.B., Salis, P.J., et al (1977) Biological Psychiatry, 12, 373.

Karacan, I., Salis, P.J., Williams, R.L. (1978), In Sleep Disorders. Diagnosis and Treatment. New York, John Wiley.

Karacan, I. (1980), Annals of Internal Medicine, 92, 334.

Kent, J.R. (1966), Diabetes, 15, 537.

Kinsey, A.C., Pomeroy, W.B., Martin, C.E. (1948), In Sexual Behaviour in the Human Male, Philadelphia, Saunders.

Kiss, F. (1921), Z. Anat., 61, 455.

Kolodny, R.C., Kahn, C.B., Goldstein, H.H., Barnett, D.M. (1974), Diabetes, 23, 306.

Kolodny, R.C., Masters, W.H., Johnson, V.E. (1979) Textbook of Sexual Medicine. Boston: Little, Brown & Co.

Kraemar, H.C., Becker, H.B., Brodie, H.K.H., et al (1976), Archives of Sexual Behaviour, 5, 125.

Kruez, L.E., Rose, R., Jennings, R. (1972), Archives of General Psychiatry, 26, 479-82.

Langeluddecke, A. (1963) Die Entmannung von Sittlichkeitsverbrechern, pp 82-85. Berlin: Walter de Gruyter.

Lawrence, D.M., Swyer, G.J.M. (1974) British Medical Journal, i, 349.

Learmouth, J.R. (1931), Brain, 54, 147.

Legros, J.J., Franchimont, P., Palemvliers, M., Servais, J. (1973), Endocrinologia Experimentalis, 7, 59.

Leriche, R. (1940), Presse Med., 48, 601.

Lester, E. (1980), British Medical Journal, iii, 354.

Lester, E., Woodroffe, F.J., Smith, R.L. (1981), Annals of Clinical Biochemistry, 18, 6.

Levine, S.B. (1976) Annals of Internal Medicine 84, 448.

McCary, J.L. (1978) McCary's Human Sexuality. New York: D van Norstrand Co.

McConnell, J., Benson, G.S., Schmidt, W.A. (1982), The Anatomical Record, 203, 475.

Marshall, P., Surridge, D.M., Delva, N. (1981), Archives of Sexual Behaviour, 10, 1.

Martin, M.M., (1953), Lancet, i, 560.

Masters, W.H., Johnson, V.E. (1979), In Textbook of Sexual Medicine, Boston, Little, Brown & Co.

May, A.G., de Weese, J.A., Rob, C.E. (1969), Surgery, 65, 41.

Melman, A., Henry, D. (1979), Journal of Urology, 121, 419.

Metz, P., Mathiesem, F.R. (1979), Vascular Surgery, 13, 70.

Michal, V., Kramer, R., Pospichal, J., Hejhal, L. (1973), Rozhl. Chir., 52, 587.

Michal, V., Pospichal, J., Lachman, M. (1976) Casopis Lekaru Ceskych, 115, 1245.

Michal, V., Kramer, R., Pospichal, J. (1978), Journal of Cardiovascular Surgery, 12, 355.

Mitamura, T. (1970), In Chinese Eunuchs, Tokyo. Charles E. Tuttle.

Montenero, P., Donatone, E. (1962), Diabetes, 10, 327.

Murawski, B.J., Chazan, B.I., Balodimos, M.C., Ryan, J.R. (1970) Diabetes, 19, 259.

Murphy, E.A. (1982) Biostatistics in Medicine. Baltimore and London: John Hopkins University Press, pp 200-229.

Nagulesparen, M., Ang, V., Jenkins, J.S. (1978), Clinical Endocrinology, 9, 73.

Naunyn, B. (1906), In Der Diabetes Mellitus, Vienna, A. Holder.

Newman, H.F., Northup, J.D. (1981), Journal of Urology, 17, 399.

von Noorden, C. (1903), In Die Zuckerkrankheit und ihre Behandlung, Berlin. A. Hirschwald.

O'Connor, V.J. (1958), Journal of Urology, 80, 195.

Ohlmeyer, P., Brilmayer, H., Hullstrung, H. (1944) Pflugers Archiv, 248, 559.

Page, M.M., Watkins, P.J. (1976), Diabetes, 25, 90.

Paz, G., Homonnai, Z.T., Drasnin, N., Safer, A., Kaplan, R., Kraicer, P.F. (1978), Andrologia, 10, 127.

Pirke, K.M., Kockott, G., Dittmar, F. (1974), Archives of Sexual Behaviour, 3, 577.

Pirke, K.M., Kockott, G. (1982). Clinics in Endocrinology and Metabolism, 11(3), 625.

de Pirro, R., Fusco, A., Spallone, L., Magnatta, R., Lauro, R. (1980), Diabetologia, 19, 118.

Polak, J.M., Gu, J., Mina, S., Bloom, S.R. (1981) Lancet, ii, 217.

Prikhozhan, V.M. (1967), Probl. Endokrinol. (Mosk), 13, 37.

Queral, L.A., Whitehouse, W.M., Flinn, W.R., Zarins, C.K., Bergan, J.J., Yao, J.S.T. (1979), Surgery, 86, 799.

Raboch, J., Mellan, J., Starka, L. (1975) Archives of Sexual Behaviour, 4, 541.

Rastogi, G.K., Chakraborti, J., Sinha, M.K. (1974), Hormone and Metabolic Research, 6, 335.

Renshaw, D.C. (1975), Diseases of the Nervous System, 36, 369.

Retief, R.J.M. (1950), South African Medical Journal, 24, 509.

Rollo, J. (1798), In Cases of the Diabetes Mellitus; with the results of the trials of certain acids and other substances in the cure of the Lues Veneria. London, C. Dilly.

Rubin, A., Babbott, D. (1958), Journal of the American Medical Association, 168, 498.

Rundles, R.W. (1945), Medicine (Baltimore), 24, 111.

Ruzbarsky, V., Michal, V. (1977), Investigative Urology, 15, 194.

Schiavi, R.C., Hogan, B. (1979), Diabetes Care, 2, 9.

Schiavi, R.C. (1980), Annals of Internal Medicine, 92, 337.

Schiavi, R.C., Fisher, C. (1982), Clinics in Endocrinology and Metabolism, 11(3), 769.

Schoffling, K. (1960), Beitr. Sexualforsch, 19, 1.

Schoffling, K., Federlin, K., Ditschuncit, H., Pfeiffer, E.F. (1963), Diabetes, 12, 519.

Schwartz, M.F., Kolodny, R.C., Masters, W.H. (1980) Archives of Sexual Behaviour, 9, 355.

Shalwan, M.M., Spathis, G.S., Fry, D.E. (1978), Diabetologia, 15, 13.

Shoukry, I., Sussett, J.G., Elhilali, M.M., Dutartre, D. (1975), British Journal of Urology, 47, 559.

Simpson, S.L. (1950), British Medical Journal, i, 692.

Spiro, M., Cotton, L.T. (1970), British Journal of Surgery, 57, 161.

Stearns, E.L., MacDonnel, J.A., Kaufman, B.J., et al (1976) American Journal of medicine, 57, 761.

Stone, C.P. (1932), In Sex and Internal Secretions, Baltimore. Williams & Wilkins Co.

Tattersall, R.B., Jackson, J.G.L. (1982) Social and emotional complications of diabetes, in: Complications of Diabetes, eds Keen, H., Jarrett, J. London: Edward Arnold, pp 271-285.

Tchobroutsky, G. (1978), Diabetologia, 15, 143.

Thorner, M.O., Besser, G.M. (1977), In Prolactin and Human Reproduction, London, Academic Press.

Treuting, T.F. (1962) American Journal of Medical Science, 94, 131.

Vermeulen, A., Rubens, R., Verdonck, L. (1972) Journal of Clinical Endocrinology and Metabolism, 34, 730.

Virag, R., Frydman, D., Cadre, N., Legman, M., Penven, J.P. (1981), Angeiologie, 33, 269.

Wagner, G., Brindley, G.S. (1980), In Vasculogenic Impotence, Illinois: Springfield, C.C. Thomas.

Wagner, G., Green, R. (1981), In Impotence, Psysiological, Psychological, Surgical Diagnosis and Treatment. New York. London. Plenum Press.

Wagner, G. (1982), Clinics in Endocrinology and Metabolism, 11, (3), 717.

Wagner, G., Bro-Rasmussen, F., Willis, E.A., Nielson, M.H. (1982), Lancet, ii, 416.

Watkins, P.J., Blainey, J.D., Brewer, D.B., Fitzgerald, M.G., Malins, J.M., O'Sullivan, D.J., Pinto, J.A. (1972), Quarterly Journal of Medicine, 41, 437.

Waxberg, J.D. (1978), Connecticut Medicine, 42, 555.Wershub, L.P. (1959) Sexual Impotence in the Male. Springfield: Illinois, Charles C. Thomas.

Whalley, L.J. (1976), In the Sexual Adjustment of Male Alcoholics. M.D. Thesis submitted to Newcastle-upon-Tyne University.

Whitelaw, G.P., Smithwick, R.H. (1951), New England Journal of Medicine, 245, 121.

Willis, E., Ottensen, B., Wagner, G., Sundler, F., Fahrenkrug, J. (1981), Acta Physiologica Scandanavica, 13, 545.

Wright, A.D., London, D.R., Holder, G., Williams, J.W., Rudd, B.T. (1976, Diabetes, 25, 975.